Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

HIV-Combination Products

AFHS classifications: 8:18.08.08 HIV Protease Inhibitors, 8:18.08.12, HIV Integrase Inhibitors, 8:18.08.16 Non-nucleoside Reverse Transcriptase Inhibitor 8:18.08.20, HIV Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Abacavir/dolutegravir/lamivudine (Triumeq)
Abacavir/lamivudine/zidovudine (Trizivir)
Abacavir/lamivudine (Epzicom)
Efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla)
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (Genvoya)
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild)
Emtricitabine/rilpivirine/tenofovir alafenamide fumarate (Odefsey)
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera)
Emtricitabine/tenofovir disoproxil fumarate (Truvada)
Emtricitabine/tenofovir alafenamide fumarate (Descovy)
Lamivudine/zidovudine (Combivir)
Atazanavir/cobicistat (Evotaz)
Darunavir/cobicistat (Prezcobix)
Lopinavir/ritonavir (Kaletra)

Final Report
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Executive Summary

Introduction: Human Immunodeficiency Virus **(**HIV) is a global public health challenge affecting more than 36 million people worldwide and 1.2 million people in the U.S. The World Health Organization (WHO) and the U.S. Department of Health and Human Services (DHHS) HIV treatment guidelines recommend that all patients living with HIV should receive antiretroviral therapy (ART) regardless of CD4 cell count in order to reduce morbidity and mortality associated with HIV-infection and prevent HIV transmission.

The goal of HIV therapy is to combine at least three antiretroviral (ARV) agents into a regimen that effectively suppresses viral replication to undetectable levels, delays disease progression, and prevents the development of resistance (also known as highly active antiretroviral therapy or HAART). According to international and national current guidelines, the standard of care for the initial treatment of HIV-infected patients (i.e treatment naïve patients) generally involves two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third ARV agent: a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor (INSTI) or a protease inhibitor (PI) boosted with a pharmacokinetic enhancer.

This report evaluates the clinical efficacy and safety of the HIV combination products based on systematic reviews, meta-analyses and randomized controlled trials (RCTs) assessing head-to-head comparisons between combination products. Currently, 14 fixed dose combination products (FDCs) available as a single pill are approved in the U.S.: Abacavir/dolutegravir/ lamivudine (ABC/DTG/3TC, Triumeq), abacavir/lamivudine/zidovudine (ABC/3TC/ZDV, Trizivir), abacavir sulfate/lamivudine (ABC/3TC, Epzicom), efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF, Atripla), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF, Genvoya), elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (EVG/c/FTC/TDF, Stribild), emtricitabine/rilpivirine/tenofovir alafenamide fumarate (FTC/RPV/TAF, Odefsey), emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF, Complera), emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada), emtricitabine/tenofovir alafenamide fumarate (FTC/TAF, Descovy), lamivudine/zidovudine (3TC/ZDV, Combivir), atazanavir/cobicistat (ATV/c, Evotaz), darunavir/cobicistat (DRV/c, Prezcobix) and lopinavir/ritonavir (LPV/r, Kaletra).

Adherence to antiretroviral regimens is crucial for HIV treatment success. Prescribed regimens may impact the effectiveness of patients' adherence to ART. Given that patients need life-long treatment, current HIV regimens are designed as single pills to reduce pill burden, improve adherence and minimize the risk of virologic failure and drug resistance.

Clinical Efficacy and Safety: Four meta-analyses and nine RCTs reporting direct head-to-head efficacy comparisons were identified for evaluation. Among the fourteen antiretroviral fixed dose combinations (FDC) available in the U.S., eight were studied in at least one comparative clinical trial. No head-to-head comparisons for initial HIV treatment were identified for the most newly approved combination products FTC/RPV/TAF (Odefsey) and FTC/TAF (Descovy), which were approved by the FDA in April 2016 and March 2016, respectively. Evidence is also lacking for ATV/c (Evotaz), DRV/c (Prezcobix), ABC/3TC/ZDV (Trizivir) and LPV/r (Kaletra). Some trials have suggested less efficacy for ABC/3TC/ZDV compared to NNRT-based regimens, and therefore it is not recommended by the U.S. guidelines. LPV/r together with 2 NRTIs is no longer recommended for initial therapy in adults due to the availability of other PIs with better safety profiles and less dosing frequency. These may be potential reasons explaining the lack of head-to-head comparisons.

Based on the evidence identified, the six following relevant drug comparisons met the criteria for inclusion. Among them, three triple fixed-dose combinations were compared to the standard of care (EFV/FTC/TDF) at the time of the study:

- Noninferiority was demonstrated for TAF/EVG/c/FTC versus TDF/EVG/c/FTC with respect to virological suppression in one meta-analysis and two clinical trials. TAF/EVG/c/FTC demonstrated a favorable renal and bone safety profile, whereas negative effects for some lipid parameters were observed in TAF/EVG/c/FTC treated patients. Long-term data showed similar efficacy and safety trends.

- One clinical trial demonstrated noninferior efficacy for TDF/EVG/c/FTC compared to EFV/FTC/TDF through week 144. A higher proportion of patients in the EFV/FTC/TDF group reported neuropsychiatric adverse effects (e.g. dizziness, abnormal dreams, insomnia), rash and lipid abnormalities (i.e. increases in HDL and LDL cholesterol concentrations) compared to the EVG/c/FTC/TDF group through week 144. These events led to drug discontinuations in that group. Nevertheless, more patients in the EVG/c/FTC/TDF group versus EFV/FTC/TDF reported nausea and renal adverse events including statistically significant elevations in serum creatinine concentration identified at week 48. A similar safety profile was observed through week 144.

- RPV/FTC/TDF was noninferior to EFV/FTC/TDF in the overall population at week 96 with respect to virological suppression, while some subgroups of patients (i.e. patients with baseline HIV RNA≤100,000 copies/mL and CD4 baseline >200 cells/µl) receiving RPV/FTC/TDF demonstrated superior efficacy compared to EFV/FTC/TDF. In the subgroup of patients with viral load >100,000 copies/mL at baseline, the RPV arm trended toward higher virologic failure rates than the EFV arm. The RPV combination reported an improved safety profile in terms of neuropsychiatric events, rash, changes in several lipid

parameters (i.e. Total, LDL and HDL cholesterol) and drug discontinuations compared to EFV combination. These results were statistically significant. By contrast, a statistically significant decreased creatinine clearance was seen in RPV/FTC/TDF compared to EFV/FTC/TDF.

- One meta-analysis and one RCT reported similar efficacy and safety conclusions when DTG plus ABC/3TC was compared to EFV/FTC/TDF. Superior efficacy and fewer discontinuations due to adverse events were reported in the DTG plus ABC/3TC group compared to EFV/FTC/TDF group through week 144.

- TDF/FTC was compared to ZDV/3TC, both in combination with EFV, in two clinical trials. Noninferior efficacy was demonstrated, although one trial reported significantly greater virological suppression with TDF/FTC versus ZDV/3TC. It should be highlighted that the primary endpoints differed in each trial. A more favorable safety profile was observed in TDF/FTC arm compared to ZDV/3TC arm. One of the trials demonstrated a statistically significant difference on the primary safety composite endpoint between groups in favor of TDF/FTC combination. Moreover, the rate for severe abnormalities was statistically significantly higher for the ZDV/3TC arm. Regarding subgroups analysis, safety profile was significantly better in women compared to men.

- TDF/FTC was compared to ABC/3TC in two meta-analyses and two RCTs. All studies reported similar efficacy, establishing the noninferiority of ABC/3TC versus TDF/FTC in terms of the proportion of patients achieving HIV-1-RNA levels <50 copies/mL. Nevertheless, one of the RCTs (i.e. the ACTG A5202 study) considered a different primary efficacy endpoint (i.e time to virologic failure) and reported different results for the two baseline HIV-RNA stratums. In the low HIV-RNA stratum noinferiority was demonstrated with respect to the time to virologic failure in any group; however, in the high HIV-RNA stratum a faster time to virologic failure was reported in ABC/3TC versus TDF/FTC with ATV/r or EFV. With respect to safety, a more favorable lipid profile was observed in TDF/FTC compared to ABC/3TC. However, some studies found more renal adverse events and greater bone mineral density reduction in the TDF/FTC group than ABC/3TC group.

Most of the trials identified included adult patients. Limited efficacy and safety data in pediatric and geriatric population was found.

Adverse Drug Reactions: The safety profile of fixed dose combinations demonstrates the adverse events specific to each component. The evidence found that combinations containing abacavir may cause hypersensitivity reactions and lipid abnormalities. Combinations containing tenofovir disoproxil fumarate are typified by renal and bone toxicity while tenofovir alafenamide may alter some lipid parameters. Efavirenz combinations are defined by neuropsychiatric, rash and lipid abnormalities. Rilpivirine combination adverse events are similar to efavirez

combinations but occur less frequently. Combination regimens including zidovudine and lamivudine are characterized by hematologic disorders (e.g anemia and neutropenia), limiting their use for HIV treatment. Integrase inhibitors coformulations including dolutegravir or elvitegravir are well-tolerated, with a lower incidence of central nervous system events than efavirenz combinations. Finally, didanosine and stavudine are NRTI agents associated with a high risk of mitochondrial toxicity, resulting in the exclusion of these agents from the fixed dose combination products and generally, from the current HIV guideline recommendations.

Summary: Fixed-dose combination products formulated as a single pill have become the current hallmark of antiretroviral treatment in HIV-infected patients. The most favorable and tolerable combination product should be individually prescribed in order to maximize the adherence to ART and therefore, reduce the morbidity and mortality associated with HIV-infection and to prevent HIV transmission.

Based on the evidence identified, six relevant fixed-dose combination comparisons met the criteria for inclusion. From an efficacy point of view, most systematic reviews and comparative randomized controlled trials showed no significant differences between FDCs. Few studies demonstrated superior efficacy of one FDC versus another FDC. The available evidence supports the current U.S. treatment guideline recommendations with respect to the recommended and alternative regimen options established for HIV treatment naïve patients. DTG/ABC/3TC was superior to EFV/FTC/TDF in the studies identified, and it is recommended by the U.S. guidelines as the preferred drug regimen if the HLA-B*5701 (a specific human genetic variation) screening test is negative. RPV/FTC/TDF was noninferior to EFV/FTC/TDF in the overall population at week 96 with respect to virological suppression, while some subgroups of patients (i.e. patients with baseline HIV RNA≤100,000 copies/mL and CD4 >200 cells/µl) receiving RPV/FTC/TDF demonstrated superior efficacy compared to EFV/FTC/TDF. RPV/FTC/TDF is classified as an alternative regimen option by U.S. guidelines for patients with HIV RNA <100,000 copies/mL and CD4 >200 cells/µl. Furthermore, several studies demonstrated noninferior efficacy of the backbone of TDF/FTC versus ABC/3TC, whereas one study indicated a more rapid time to virologic failure for ABC/3TC plus ATV/r or EFV compared to TDF/FTC plus ATV/r or EFV in patients with HIV RNA<100,000 copies/mL. Current guidelines consider TDF/FTC as recommended backbone when combined with dolutegravir, elvitegravir/cobicistat, raltegravir or darunavir/ritonavir. ABC/3TC is also considered a recommended backbone in combination with dolutegravir if HLA-B*5701 test is negative. In addition, ABC/3TC is considered as “other regimen option” backbone for patients with HIV RNA<100,000 copies/mL and HLA-B*5701 negative when combined with efavirenz, atazanavir/ritonavir, atazanavir/cobicistat and raltegravir. Use of a ZDV/3TC backbone resulted in similar or reduced efficacy and a worse safety profile compared to TDF/FTC. Current guidelines do not recommend the use of a ZDV/3TC backbone for non-pregnant adults. However, it is considered an

alternative regimen for children and pregnant women. If tenofovir is included as part of an antiretroviral (ARV) combination, it should be considered that TAF-containing combinations have demonstrated similar efficacy, better renal and bone safety profiles, and higher incidence of lipid abnormalities compared to TDF-containing combinations. TAF/FTC, RPV/FTC/TAF, ATV/c and DRV/c are recommended by current guidelines, based on switching or bioequivalence studies, but no direct head-to-head comparisons with a single tablet formulation have been identified. Evidence is also lacking for ABC/3TC/ZDV and LPV/r. ABC/3TC/ZDV is not recommended by the U.S. guidelines and LPV/r is only recommended in some specific groups of patients such as children and pregnant women.

The safety profile of ARV fixed dose combination products is characterized by the adverse events specific to each component. Treatment decisions should be based on individual patient characteristics including comorbidities, drug interactions, drug resistance and potential toxicities derived from the drugs.

Adherence to antiretroviral drugs is crucial to accomplish HIV treatment success. Before initiation of ART, patient education should outline the importance of adherence in order to avoid drug-resistance, maintain maximal virological suppression, and ultimately, improve quality of life. Numerous studies have demonstrated increased adherence rates in patients receiving treatment with single-tablet regimens compared to those on multiple-tablet regimens.

Introduction

Human immunodeficiency virus (HIV) infection is a life-threatening and serious infectious disease that can progress to the acquired immune deficiency syndrome (AIDS).[1,2] HIV constitutes a global public health challenge. In 2015, approximately 36.7 million people worldwide were affected.[3] The World Health Organization (WHO) and the U.S. Department of Health and Human Services (DHHS) HIV treatment guidelines recommend that all patients living with HIV should receive Antiretroviral Therapy (ART) regardless of CD4 cell count[4] in order to reduce the morbidity and mortality of HIV-infection and to prevent HIV transmission.[5,6] Globally, data from mid-2016 report that 18.2 million people living with HIV were receiving ART.[6]

Antiretroviral (ARV) agents used in the treatment of HIV infection act by inhibiting various steps in the HIV replication cycle, and include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (EIs), fusion inhibitors and integrase inhibitors (INSTIs). Appendix A provides a summary of the drug classes and U.S. Food and Drug Administration (FDA) ARV agents used in the treatment of HIV-1 infection.

The goal of HIV therapy is to combine at least three antiretroviral (ARV) agents into a regimen that effectively suppresses viral replication to undetectable levels, delays disease progression and prevents the development of resistance (also known as highly active antiretroviral therapy or HAART). According to international and national published guidelines,[5,7] the standard of care for the initial treatment of HIV-infected patients generally involves two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third ARV agent: a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor (INSTI) or a protease inhibitor (PI) boosted with a pharmacokinetic enhancer, cobicistat or ritonavir.[5,7,8]

This report evaluates the clinical efficacy and safety of the HIV combination products based on systematic reviews, meta-analyses and randomized controlled trials (RCTs). Currently, 14 fixed-dose combination products available as a single pill are approved in the U.S.: Abacavir/Dolutegravir/Lamivudine (ABC/DTG/3TC, Triumeq), Abacavir/Lamivudine/Zidovudine (ABC/3TC/ZDV, Trizivir), Abacavir sulfate/Lamivudine (ABC/3TC, Epzicom), Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF, Atripla), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/c/FTC/TAF, Genvoya), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/c/FTC/TDF, Stribild), Emtricitabine/Rilpivirine/Tenofovir Alafenamide Fumarate (FTC/RPV/TAF, Odefsey), Emtricitabine/Rilpivirine /Tenofovir Disoproxil Fumarate (FTC/RPV/TDF, Complera), Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF,

Truvada), Emtricitabine/Tenofovir Alafenamide Fumarate (FTC/TAF, Descovy), Lamivudine/Zidovudine (3TC/ZDV, Combivir), Atazanavir/Cobicistat (ATV/c, Evotaz), Darunavir/Cobicistat (DRV/c, Prezcobix) and Lopinavir/Ritonavir (LPV/r, Kaletra).[9-11]

Fixed-dose combination products (FDCs) formulated as a single pill have become the current hallmark of antiretroviral treatment in HIV-infected patients. The most appropriate and tolerable combination product(s) should be prescribed in order to maximize adherence to ART and consequently, reduce the morbidity and mortality associated with HIV-infection, and prevent HIV transmission. The first combination product available in the U.S. to treat HIV infection was 3TC/ZDV, approved in September 1997 by the Food and Drug Administration (FDA).[11] The most recent FDC is FTC/TAF (Descovy), approved in April 2016 by the FDA. NRTIs are usually prescribed in pairs and designated as the "backbone"of ART regimens.[12] FTC/TDF (Truvada) or FTC/TAF (Descovy) and ABC/3TC are considered the recommended backbones in the current U.S. guidelines, administered in combination with a third ARV agent. Likewise, triple FDC such as DTG/ABC/3TC (Triumeq), EVG/c/FTC/TAF (Genvoya) or EVG/c/FTC/TDF (Stribild) are considered the recommended complete regimens for treatment-naïve patients.[5,10,11]

Table 1 provides a summary of the FDA-approved products, dosage forms, labeled indications, dosing recommendations and generic availability of the combination products. In general, all FDCs are administered orally and are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents or available as complete regimens. FTC/TDF is also indicated for pre-exposure prophylaxis (PrEP).[11] One of the most relevant advantages of the FDCs is related to the reduction in daily pill burden, and improvement in adherence to ART. Most of the FDCs are administered once daily, with the exception of 3TC/ZDV and ABC/3TC/ZDV that are administered twice daily.[10,11]

According to Utah Medicaid fee-for-service (FFS) claims data, the FDC most frequently prescribed by physicians during 2016 was Truvada (FTC/TDF, 35%), followed by Triumeq (ABC/DTG/3TC, 19%), Atripla (EFV/FTC/TDF, 16%), Genvoya (EGV/C/FTC/TAF, 7%), Stribild (EGV/C/FTC/TDF, 7%) and Epzicom (ABC/3TC, 6%). Less than 5% of claims were for Complera (FTC/RPV/TDF), Kaletra (LPV/r), Descovy (FTC/TAF) or 3TC/ZDV (Combivir Generic). No FFS Medicaid patient drug claims were reported for Trizivir (ABC/3TC/ZDV), Odefsey (FTC/RPV/TAF), Evotaz (ATZ/c) or Prezcobix (DRV/c).

Table 1. FDA Approved Combination Products for the Treatment of HIV-1[9-11]

Active substances	Available dosage forms (Generic, if available)	Dosing Recommendations	Indications	Approval date
Abacavir/Dolutegravir/Lamivudine (ABC/DTG/3TC) Triumeq®	Tablets: ABC 600 mg plus 3TC 300 mg plus DTG 50 mg	Adults: 1 tablet QD TRIUMEQ should not be used in children. *Note*: Prior to initiation or re-initiation of therapy, screen for the HLA-B*5701 allele due to ABC	Treatment of HIV-1 infection Limitations of Use: • TRIUMEQ alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ. • TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations.	08/22/2014
Abacavir sulfate/Lamivudine (ABC/3TC) Epzicom®	Film-coated tablet: ABC 600 mg plus 3TC 300 mg *(Generic available)*	Adults: 1 tablet QD Pediatric patients (≥25 kg): 1 tablet QD *Note*: Prior to initiation or re-initiation of therapy, screen for the HLA-B*5701 allele due to ABC	Treatment of HIV-1 infection in combination with other antiretroviral agents	08/02/2004
Abacavir/Lamivudine/Zidovudine (ABC/3TC/ZDV) Trizivir®	Tablets: ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg	Adults and adolescents ≥40 kg: 1 tablet BID *Note*: Prior to initiation or re-initiation of therapy, screen for the HLA-B*5701 allele due to ABC	Treatment of HIV-1 infection in combination with other antiretroviral agents Unlabeled indication: nPEP	11/14/2000
Atazanavir/Cobicistat ATV/c Evotaz®	Tablets: ATV 300 mg plus COBI 150 mg	Adults: 1 tablet QD *Note*: Assess CrCl prior to initiation	Treatment of HIV-1 infection in adults, in combination with other antiretroviral agents Limitations of use: Use in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions	01/29/2015
Darunavir/Cobicistat DRV/c Prezcobix®	Tablets: DRV 800 mg plus COBI 150 mg	Adults: 1 tablet QD *Note*: Assess CrCl. Genotype testing is advised prior to therapy initiation in antiretroviral treatment-experienced patients.	Treatment of HIV-1 infection in adult patients	01/29/2015
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate EFV/FTC/TDF Atripla®	Tablets: FTC 200 mg, EFV 600 mg, TDF 300 mg	Adults and ≥12 years (≥40 kg): 1 tablet at or before bedtime *Note*: test for presence of HBV and assessment of CrCl, serum phosphorus, urine glucose, and urine protein prior to initiation	Alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older	07/12/2006

Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Fumarate EVG/c/FTC/TAF Genvoya®	Tablets: FTC 200 mg, EVG 150 mg, COBI 150 mg, TAF 10 mg	Adults and ≥12 years (≥35 kg): 1 tablet QD *Note*: Test for HBV infection prior to initiating therapy; severe acute HBV exacerbations have occurred following discontinuation of products containing FTC and/or tenofovir in patients coinfected with HIV and HBV	As a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of GENVOYA	11/05/2015
Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate EVG/c/FTC/TDF Stribild®	Tablets: FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg	Adults: 1 tablet QD *Note*: Test for HBV infection prior to initiating therapy; severe acute HBV exacerbations have occurred following discontinuation of products containing FTC and/or tenofovir in patients coinfected with HIV and HBV	Complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD Unlabeled indication: oPEP	08/27/2012
Emtricitabine/Rilpivirine/Tenofovir Alafenamide Fumarate FTC/RPV/TAF Odefsey®	Tablets: FTC 200 mg plus RPV 25 mg plus TAF 25 mg	Adults and ≥12 years (≥35 kg): 1 tablet QD *Note*: Test for presence of HBV and CrCl must be ≥ 30 mL/min before initiation of treatment	As a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of ODEFSEY	03/01/2016
Emtricitabine/Rilpivirine /Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) Complera®	Tablets: FTC 200 mg, RPV 25 mg, TDF 300 mg	Adults and ≥12 years (≥35 kg): 1 tablet QD	As a complete regimen for the treatment of HIV-1 infection in (1) patients 12 years of age and older with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and (2) in certain virologically suppressed (HIV-1 RNA <50 copies/mL) patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen. *Note*: Please see the package information to check the points that should be met when considering replacing the current regimen with COMPLERA in virologically-suppressed (HIV-1 RNA <50 copies/mL) patients Unlabeled indication: Prophylaxis of perinatal transmission	08/10/2011
Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)	Film-coated tablet: 200 mg/300 mg 167 mg/250 mg 133 mg/200 mg	**Treatment of HIV-1 Infection:** Adults and pediatric patients ≥35 kg: 1 tablet (200 mg/300 mg) QD	Treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg.	08/02/2004

Truvada®	100 mg/150 mg of FTC and TDF	Pediatric patients ≥ 17 kg: 1 tablet (100 mg/150 mg, 133 mg/200 mg, or 167 mg/250 mg based on body weight) QD **Pre-exposure Prophylaxis:** Adults**:** 1 tablet (200 mg/300 mg) QD	Indicated in combination with safer sex practices for **pre-exposure prophylaxis (PrEP)** to reduce the risk of sexually acquired HIV-1 in adults at high risk Unlabeled indication: - oPEP and nPEP - Treatment of hepatitis B in patients with antiviral-resistant HBV or coinfection with HIV	
Emtricitabine/Tenofovir Alafenamide Fumarate (FTC/TAF) Descovy®	Tablet: FTC 200 mg plus TAF 25 mg	Adults and ≥12 years (≥35 kg): 1 tablet QD *Note*: Test for presence of HBV and CrCl must be ≥30 mL/min before initiation of treatment	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older in combination with other antiretroviral agents Limitations of Use: DESCOVY is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.	04/04/2016
Lamivudine/Zidovudine 3TC/ZDV Combivir®	Tablets: 3TC 150 mg plus ZDV 300 mg *(Generic available)*	Adults and adolescents ≥ 30 kg: 1 tablet BID Pediatric patients ≥ 30 kg: 1 tablet BID	Treatment of HIV-1 infection in combination with other antiretroviral agents Unlabeled indication: - oPEP - Prophylaxis of perinatal transmission	09/26/1997
Lopinavir/Ritonavir LPV/r Kaletra®	Tablets: LPV 200 mg plus RTV 50 mg Tablets: LPV 100 mg plus RTV 25 mg Oral solution: LPV 80 mg/mL plus RTV 20 mg/mL *(Generic available)*	Adults: • LPV 400 mg plus RTV 100 mg BID • LPV 800 mg plus RTV 200 mg QD Pediatric patients: BID dosing based on body weight or body surface area (*See Full Prescribing Information for details*) *Note*: **do not use QD dosing** in patients with 3 or more lopinavir resistance-associated substitutions, in patients receiving concomitant therapy with nevirapine, efavirenz, nelfinavir, carbamazepine, phenobarbital, or phenytoin; in pregnant women and in pediatric patients (≥ 14 days, < 18 years)	Treatment of HIV-1 infection in adults and pediatric patients (14 days and older) Unlabeled indication: - HIV-1 nPEP (children) - Prophylaxis of postnatal transmission - Severe acute respiratory syndrome	09/15/2000

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BID= twice daily; COBI or c = cobicistat; d4T = stavudine; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; FDA= Food and Drug Administration; HBV = hepatitis B virus; nPEP= nonoccupational Postexposure Prophylaxis; oPEP= occupational Postexposure Prophylaxis; QD= Once a day; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF= tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Disease Overview

Human immunodeficiency virus (HIV) is a lentivirus within the family of mammalian retroviruses.[1] Two types of virus have been recognized (HIV-1 and HIV-2), although the majority of human infection is caused (or produced) by HIV-1.

The life cycle of HIV include six steps: entry into immune cells through binding to CD4 receptors and fusion; reverse transcription of viral RNA into DNA using HIV reverse transcriptase enzymes; integration of viral DNA into the DNA of the CD4 cell by HIV integrase enzymes; replication (transcription and translation); assembly; and budding and maturation using HIV protease enzymes.[12-15]

The course of untreated HIV infection in adults is well-described. HIV infection generally begins with an acute retroviral illness several weeks after infection associated with a rapid increase of HIV RNA copies and decline of CD4 T-cell count. The disease progresses to a long, asymptomatic period (clinical latency stage) where the immune system controls the virus during the initial years. As the immune system becomes significantly compromised, the symptomatic stage starts with mild symptoms, followed by opportunistic diseases (AIDS stage). In untreated patients, HIV infection may lead to death.[2]

Both the United States Centers for Disease Control and Prevention (CDC)[16] and the World Health Organization (WHO)[17] have published staging systems for adolescent and adult patients with HIV/AIDS to help identify disease severity and guide decisions concerning prophylactic treatment and the initiation of ART. The CDC staging system defines three categories of CD4 counts with HIV clinical symptoms while the WHO outlines four clinical stages for presenting symptoms.

Epidemiology

HIV infection is a worldwide health challenge. Approximately 36.7 million people were living with HIV at the end of 2015 with Sub-Saharan Africa the most affected region (25.6 million people).[3,18] Among them, 2.1 million people were newly infected in 2015. From 2000 to 2015, new HIV infections and AIDS-related deaths have dropped by 35% and 28%, respectively.[6]

In the United States, more than 1.2 million people are living with HIV infection and approximately 50,000 new HIV infections are diagnosed each year.[19] Deaths relating to HIV infection peaked in 1995. Since 1995, deaths related to HIV have decreased approximately 70% coincident with the introduction of ART.[1] From 2005 to 2014, a 19% reduction in the number of new HIV diagnoses was observed. In 2015, demographic groups at highest risk of becoming infected include men who have sex with men, heterosexual women, injection drug users, African Americans, Hispanics/Latinos, and people aged 20-29 years. Geographically, the southern United States reports the highest rate of new HIV cases.[20]

In Utah, the total number of people living with HIV at the end of 2015 was 2,934. Among them, 47% were adults between 45-59 years, 35% were between 22-44 years, 17% were ≥60 years old and 1% were children or adolescents. The majority of HIV infected individuals were males (85%) and the most

common route of HIV transmission was male-to-male sexual contact (65%).[21] The rate of newly-diagnosed HIV cases in Utah during 2015 was 4 per 100,000 population. The most commonly affected were adult males aged 25-44 years (68%) and non-Hispanic white persons (59%). Hispanic blacks and Hispanics were disproportionately affected. The rate in males has been increasing from 2011 to 2015 (89 new cases to 108 new cases yearly, respectively). The rate of new HIV cases in Utah females remains stable. The main routes of HIV transmission in Utah in 2015 were male-to-male sexual contact (58%) followed by injection drug use (11%) among males, and unprotected sex with a male partner (67%) and injection drug use (17%) among females.[22]

Clinical Guidelines for the Management of HIV-Infection

The primary objectives of ART treatment include suppressing the viral load to undetectable levels, increasing the CD4 cell count, preventing the development of opportunistic infections, avoiding the emergence of viral resistance and preventing HIV transmission.[5] To achieve these goals, the approach called HAART recommended by international, European and American guidelines for the use of antiretroviral agents[5,7,8,23] should be given to all HIV-positive patients. Moreover, initiation of ART is recommended as soon as possible after diagnosis and regardless of CD4 cell count[4] or disease stage.[5]

Before initiation of ART, the patient should be medically and psychosocially prepared. U.S.Department of Health and Human Services guidelines recommend the use of genotypic drug-resistance testing to guide therapy decisions. Moreover, screening for HLA-B*5701 prior to initiation of abacavir-containing regimens is recommended to diminish the risk of serious hypersensitivity reactions. In an attempt to reduce or avoid drug-resistance, patients should receive education and counseling outlining the advantages and disadvantages of therapy and the importance of adherence before initiation of therapy. If the benefits do not outweigh the risks or if adherence will be a significant challenge, patients may decide to postpone therapy or providers may recommend deferring therapy.[5,8] However, treatment should be initiated as soon as possible.

Once treatment is initiated, the goals become achieving viral suppression below detection limits, reducing the risk of disease progression and preventing HIV transmission. Initial therapy is individualized according to virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, and genotypic resistance test results to accomplish these goals. In addition, promoting adherence to treatment plays an important role in long-term viral suppression maintenance (treatment success).[5,24] Several studies have demonstrated that once-daily antiretroviral regimens and regimens with low pill burden increase adherence rates and treatment success.[25-28] Thus, fixed dose drug combinations are recommended to be prescribed whenever feasible.[5]

In general, the recommendations for initiation of ART and goals of therapy in adults and adolescents are the same for special populations with HIV infection. **Table 4** describes the main recommendations for NRTIs in special populations. Individual patient characteristics should be considered before starting ART. Pharmacokinetics, potential drug interactions and specific drug

toxicities are some of the factors that impact treatment decisions for which dosage adjustments may be required.

The most recent clinical practice guidelines available concerning ART combination therapy recommendations are summarized in Table 2. Only recommendations from the DHHS and WHO for patients who have not received prior ART therapy have been condensed. References for other HIV guidelines are presented in the Table 2. Overall, an ARV regimen for treatment-naive patients generally consists of a three drug combination including two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug , an NNRTI, INSTI or boosted PI[5]. Recommended regimens were selected based on durable virologic efficacy, ease of use, and favorable tolerability and toxicity profiles. However, alternative regimens could be the best option for individual patients. According to the DHHS guidelines for adults and adolescents,[5] the International Antiviral Society-USA Panel (IAS-USA)[23] and the European AIDS Clinical Society (EACS)[8] guidelines, the most commonly used NRTIs backbones in the preferred or alternative regimens are ABC/3TC, TDF/FTC or TAF/FTC. Moreover, all guidelines for adults prefer regimens containing an integrase inhibitor. DHHS guidelines include an INSTI (i.e. Dolutegravir or elvitegravir) or a boosted PI (i.e. Darunavir/ritonavir) as the third preferred agent. In contrast, EACS guidelines also include a NNRTI (i.e. Rilpivirine) or another PI (i.e. Darunavir/cobicistat) as preferred third agents. The International Antiviral Society-USA Panel (IAS-USA) and DHHS guidelines offer similar treatment recommendations, although IAS-USA consider darunavir/ritonavir plus TAF (or TDF)/FTC as an alternative option in those patients where an INSTI is not an option.

Table 2. Guidelines for the Management of HIV-1 with Antiretroviral Therapy

Guideline	Recommendations for Treatment Naïve Patients
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (US Department of Health and Human Services (DHHS Panel on Antiretroviral Therapy, National Institutes of Health Office of AIDS Research Advisory Council, July 2016)[5] *Note*: Guideline applies to post-pubertal adolescents, sexual maturity rating IV and V, and adults	**Recommended regimens** • INSTI + 2-NRTIs: – DTG/ABC/3TC[a] - only if HLA-B*5701 negative – DTG + [TDF/FTC[a]] or [TAF/FTC] – EVG/c/TDF/FTC or EVG/c/TAF/FTC – RAL + [TDF/FTC[a]] or [TAF/FTC] • Boosted PI + 2 NRTIs: – DRV/r + [TDF/FTC[a]] or [TAF/FTC] **Alternative regimens** • NNRT + 2 NRTIs: – EFV/TDF/FTC[a] – EFV + TAF/FTC – RPV/TDF/FTC[a] or or RPV/TAF/FTC - only for patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3 • Boosted PI + 2 NRTIs: – (ATV/c or ATV/r) + TDF/FTC[a] or TAF/FTC – (DRV/c or DRV/r) + ABC/3TC[a] only if HLA-B*5701 negative – DRV/c + TDF/FTC[a] or TAF/FTC **Other regimens** • If HIV RNA <100,000 copies/mL and HLA-B*5701 Negative: – (ATV/c or ATV/r) + ABC/3TC – EFV + ABC/3TC[a] – RAL + ABC/3TC[a] • Other regimens to consider when TAF, TDF, or ABC cannot be used: – DRV/r + RAL (BID) – only if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3 – LPV/r + 3TC[a] (BID) *Note*: When choosing between an INSTI, NNRTI, or PI as the third drug, the patient's comorbidities, concomitant medications, and the potential for non-adherence to the regimen should be considered
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (DHHS Panel on Antiretroviral Therapy, National Institutes of Health Office of AIDS Research Advisory Council, March 2016) [24] *Note*: Guideline applies to post-pubertal adolescents, sexual	**Preferred 2-NRTI backbone** for use in combination: – <3 months: ZDV + (3TC or FTC) – ≥3 months and <12 years: ABC + (3TC or FTC) or ZDV + (3TC or FTC); ABC – ≥12 years and SMR I-III: ABC + (3TC or FTC) or TAF/FTC – ≥12 years and SMR IV-V: Refer to ART guideline for adults and adolescents[5] **Alternative 2-NRTI backbone** for use in combination: – ≥2 weeks: ddI + (3TC or FTC) or ZDV + ddI – ≥3 months: ZDV plus ABC – Adolescents at SMR III: TDF + (3TC or FTC) – ≥12 years at SMR III: ZDV + (3TC or FTC) **Other 2-NRTI backbone** for use in special circumstances in combination: – TDF + (3TC or FTC) **Preferred third agents** to combine with backbone: – ≥42 weeks postmenstrual and ≥14 days postnatal, and <3 years: LPV/r – ≥2 years to <3 years: LPV/r or RAL – ≥3 years to <12 years: ATV/r, DRV/r BID, EFV, LPV/r or RAL

maturity rating (SMR) 3 and below	– ≥12 years and SMR I-III: ATV/r, DTG, DRV/r QD or EVG/c – ≥12 years and SMR IV-V: Refer to ART guideline for adults and adolescents[5] **Alternative third agents** to combine with backbone: – >14 days old <3 years: NVP – ≥4 weeks to <2 years and ≥3 kg: RAL – ≥3 months to <3 years and ≥10 kg: ATV/r – ≥12 years and SMR I-III: EFV, RAL, RPV
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal health and Interventions to Reduce Perinatal HIV Transmission in the United States (DHHS Panel on Antiretroviral Therapy, National Institutes of Health Office of AIDS Research Advisory Council, October 2016)[29]	**Preferred Initial Regimens in Pregnancy** Preferred 2-NRTI Backbones – ABC/3TC ▪ HLA-B*5701 should be negative ▪ Do not use ABC/3TC with ATV/r or with EFV if pretreatment HIV RNA >100,000 copies/mL – TDF/FTC or TDF/3TC: caution in patients with renal toxicity Preferred PI Regimens – ATV/r + a Preferred 2-NRTI Backbone (neonatal bilirubin monitoring recommended) – DRV/r + a Preferred 2-NRTI Backbone Preferred INSTI Regimens – RAL + a Preferred 2-NRTI Backbone **Alternative Initial Regimens in Pregnancy** Alternative 2-NRTI Backbones – ZDV/3TC Alternative PI Regimens – LPV/r + a Preferred 2-NRTI Backbone Alternative NNRTI Regimens – EFV + a Preferred 2-NRTI Backbone: ▪ Cautionary text about birth defects appears in the package insert. Preferred regimen in women who require coadministration of drugs with significant interactions with PIs or the convenience of coformulated, single tablet, once-daily regimen. Screening for antenatal and postpartum depression is recommended. – RPV/TDF/FTC (or RPV + a Preferred 2-NRTI Backbone) ▪ Do not use if pretreatment HIV RNA >100,000 copies/mL *Note*: Avoid the use of d4T, ddI and RTV due to toxicity
Consolidated Guidelines on Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach (World Health Organization; June 2016)[7]	**First Line ART for Adults** (including pregnant/nursing women) • Should include 2-NRTI backbone plus an NNRTI or INSTI • Fixed dose combinations and once-daily regimes are preferred – TDF +EFV + (3TC or FTC) • If the above is unavailable or contraindicated choose from the following: - AZT + 3TC + (EFV or NVP) - TDF + (3TC or FTC) + NVP - TDF + (3TC or FTC) + (DTG or $EFV_{400mg/d}$) **First Line ART for Adolescents** (10 to 19 years) - Preferred: TDF + (3TC or FTC) + EFV as a fixed-dose combination - Alternative: TDF + (3TC or FTC) + (DTG or $EFV_{400mg/d}$) • If the above regimens are unavailable or contraindicated then the following are alternative options: - ABC + 3TC + (EFV or NVP)

	- AZT + 3TC + (EFV or NVP) - TDF + (3TC or FTC) + NVP **First Line ART for Children** (Age 3 and up to 10 years old, weighing <35 kg) - Preferred NRTI backbones: [ABC + 3TC] or [(AZT or TDF) + (3TC or FTC)] - Preferred NNRTI: EFV or Alternative NNRTI: NVP **First Line ART for Children less than 3 years old** - Preferred NRTI backbone (ABC or AZT) + 3TC combined with LPV/r - Alternative: (ABC or AZT) +3TC + NVP - Consider substituting LPV/r with EFV at 3 years-old <u>NNRTI place in therapy when the above first line regimens have been exhausted</u>: • May consider second-generation NNRTIs with minimal risk of cross-resistance as third-line (low-quality evidenced based recommendation) **Infant Prophylaxis** • Infants born to mothers with HIV at high risk of contracting HIV - AZT + NVP for first 6 weeks of life • Breastfed infants of mother with HIV receiving ART - NVP for 6 weeks
Other Guidelines Available:	**Department of Health and Human Services**[30] • Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Updated 11/2016 • Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children, Updated 12/2016 **International Antiviral Society- USA Panel** • Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults, 2016[23] **Centers for Disease Control and Prevention**[31] • Recommendations for HIV Prevention with Adults and Adolescents with HIV in the United States, 2014 • Pre-exposure Prophylaxis for the Prevention of HIV in the United States: A Clinical Practice Guideline, 2014 • Updated Guidelines for Antiretroviral Post-exposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-occupational Exposure to HIV— United States, 2016 **Infectious Disease Society of America**[32] • Clinical Practice Guideline for The Management of Chronic Kidney Disease in Patients Infected with HIV, 2014 • Primary Care Management of HIV-Infected Patients, 2013 • Prevention and Treatment of Opportunistic Infections, 2015 **European AIDS Clinical Society (EACS)**[8] • European AIDS Clinical Society Guideline (version 8.2, January 2017)

[a]3TC may be substituted for FTC, or vice versa, if a non-fixed dose NRTI combination is desired.

Key to Abbreviations: 3TC=lamivudine, ABC=abacavir, ART=Antiretroviral Therapy, ATV=atazanavir, AZT=zidovudine, BID=twice daily, c=cobicistat, COBI=cobicistat, d4T=stavudine, ddl=didanosine, DHHS=Department of Health and Human Services, DVL=delavirdine, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, EVG=elvitegravir, FTC=emtricitabine, INSTIs=integrase strand transfer inhibitors, LPV=lopinavir, NIH=National Institutes of Health, NNRTIs=non-nucleoside reverse transcriptase inhibitors, NRTIs=nucleoside/nucleotide reverse transcriptase inhibitors, NVP=Nevirapine, PI=protease inhibitor, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SAQ=saquinavir, SMR=Sexual Maturity Rating, TAF=tenofovir alafenamide, TDF=tenofovir disoproxil, ZDV or AZT=zidovudine

Adherence to antiretroviral treatment

Adherence to ARV drugs is crucial to achieve effective virological suppression in HIV-infected patients, to improve quality of life, to prevent HIV transmission, to avoid drug resistance and finally, and to increase survival.[25] The principal cause of treatment failure is poor adherence to treatment.[5] Given that ART is a life-long treatment that requires daily ARV drug administration,[33] current HIV treatments are designed to improve adherence and minimize the risk of virologic failure and drug resistance.[5]

There are several limitations to the effectiveness of adherence to ART. The social and clinical situation of patients, the prescribed regimen, the information about the importance of ART compliance as well as counseling provided by the HIV healthcare provider, and the patient engagement are the most relevant factors influencing adherence to treatment.[5,33]

The development of effective adherence programs has increased the success of HIV treatment. Strategies that improve adherence and retention in care, include an accessible, trustworthy health care team, strengthened early linkage to care and retention in care, assessment of patient readiness to start ART, identification of the type of and reasons for nonadherence, and selection of the most appropriate treatment adherence intervention(s) to meet individual patient needs.[5]

Numerous studies have analyzed the relationship between pill burden and the level of adherence to ART. Others have compared the adherence of single tablet-fixed dose combinations administered once daily to ARV combinations administered more than once a day.

Clay et al[25] performed a meta-analysis including 9 studies to compare single and multi-tablet fixed dose combinations. Results reflected significantly better viral suppression and adherence in those patients receiving single-tablet FDCs once daily than the group receiving multiple-tablet FDCs requiring multiple dosing times or units per day (adherence outcomes: odds ratio (OR) 2.37, 95% CI [1.68 to 3.35]; $p<0.001$; viral load suppression at week 48: RR 1.09, 95% CI [1.04-1.15], $p=0.0003$). Likewise, severe laboratory abnormalities were statistically significantly lower in the single tablet FDC arm. Tolerability, safety outcomes and mortality were similar between groups. From an economic point of view, this study demonstrated reduced healthcare resource utilization and mean costs in the groups of patients receiving single-tablet regimens than in those on multiple-tablet treatment.

Nachega et al[26] performed a meta-analysis of 19 studies to explore the relationship between pill burden and ART adherence. The study found lower adherence and worse virologic suppression with higher pill burden. Moreover, patients receiving once daily regimens showed better adherence than those on twice-daily regimens (mean difference: 2.55%; 95% CI 1.23 to 3.87; $p=0.0002$), although virological suppression was reported to be similar between groups.

Ramjan et al[27] performed a meta-analysis of 21 studies (including RCTs and observational studies) to investigate the benefits for patients and care programs between FDCs and separate tablets regimens. RCTs indicated a tendency towards better adherence (RCTs: 1.10; 95% CI 0.98-1.22) and virological suppression in those patients receiving FDCs regimens versus those on treatment with separate tablets regimens. However, a statistically significant difference in relative risk was only observed when evaluating adherence to ART in observational studies (RR 1.17, 95% CI 1.07-1.28). The most common FDC studied was efavirenz/emtricitabine/tenofovir followed by abacavir/lamivudine.

Sterrantino et al[34] studied the self-reported adherence to single-tablet regimens and to ART containing ritonavir-boosted PIs, NNRTIs, raltegravir or maraviroc. Nonadherence was lowest in patients receiving single tablet regimens (17.4%, $p<0.05$) with an OR of 0.45 (95% CI: 0.22-0.92).

Parienti et al[28] demonstrated in a meta-analysis of 11 randomized controlled trials that once-daily regimens were associated with a significantly better adherence rate than twice daily regimens (+2.9%; 95% CI 1.0% to 4.8%; $p<0.003$).

Langebeek et al[35] carried out a meta-analysis to evaluate the predictors of adherence to ART, and found that adherence is significantly correlated to patient psychological factors (e.g. self-efficacy, concerns and beliefs about ART, trust in healthcare providers, etc.). Furthermore, evidence suggested that an increase in pill burden or daily dosing may lead to lower adherence rates.

Authors of one one observational study[36] found that single-tablet regimens are associated with less risk of hospitalizations and a higher probability of viral suppression success.

In summary, single-tablet regimens are simplified regimens that provide improved adherence and a trend toward better virological suppression with respect to other combination ARTs administered as separate tablets or as twice-daily regimens. This insight constitutes a benefit for patients and HIV healthcare programs.

Pharmacology

The mechanisms of action of the fixed-dose, co-formulations of ART reflect the different ARV classes within the FDCs. Combining medications with different mechanisms of action provides potent ARV FDCs that effectively inhibit the viral replication, prevent the emergence of resistance and increase adherence.

Pharmacokinetic properties vary among the fourteen FDA approved combination ARV products. Generally, the main advantage of dual and triple, fixed-dose combinations is that they are administered once daily, with demonstrated improvement in adherence in several meta-analyses.[25,26,28] Only abacavir/lamivudine/zidovudine, lamivudine/zidovudine and lopinavir/ritonavir are administered twice daily.[10,11] **Table 3** summarizes the pharmacokinetic properties of the combination products available in the U.S.

Drug Interactions

The complexity of antiretroviral interactions involves the existence of several drug metabolic pathways, the use of multiple, interacting ARV drugs in combination, the use of additional medications for comorbid medical conditions, and limited pharmacokinetic interaction studies, among others.[37] When initiating or switching combination ART regimens, information concerning drug-drug interactions should be carefully assessed with a clinical HIV specialist or using a drug-drug interaction database to avoid potential drug toxicities. Underdosing or overdosing may result from the increase or decrease of ARV levels by interacting medications or changes in metabolism or excretion.[37,38] Aside from careful regimen adjustment due to interacting drugs, dosage adjustment may be required in patients with renal or hepatic impairment, in pediatric or in geriatric patients.

Recommended regimens for the management of HIV-infection include a combination of two NRTIs plus one NNRTI, one INSTI, or a PI boosted with a pharmacokinetic enhancer. The majority of antiretroviral drugs, especially PIs, NNRTIs, cobiscistat (pharmacokinetic booster) and maraviroc (CCR5 receptor antagonist) can interfere or be affected by the hepatic drug metabolism through hepatic cytochrome (CYP) P450 enzyme or by other drug pharmacokinetic pathways.[37]

NRTI agents are mainly excreted in the urine.[39] They are not substrates, inducers or inhibitors of hepatic cytochrome P450 (CYP). Hence, serious clinical drug-drug interactions mediated through CYP enzymes are unlikely.[12] Emtricitabine, lamivudine and tenofovir are mainly eliminated unchanged in the urine through glomerular filtration and active tubular secretion. Zidovudine is metabolized through glucuronidation. NRTIs may potentially interact with other drugs eliminated by the same pathway.[40] Additionally, NRTIs are prodrugs requiring

intracellular phosphorylation for transformation to the active form. Drugs that compete for the same intracellular pathways, may affect the plasma concentrations of active NRTIs.[39]

NNRTIs may be involved in many drug interactions, since the CYP enzymes mediate their metabolism. For instance, efavirenz is metabolized via CYP2B6 and is also an inducer of CYP3A4.[5,38]

INSTIs do not interact at CYP3A4, but dolutegravir and elvitedravir are CYP3A4 substrates. Raltegravir and dolutegravir are primarily metabolized by UGT1A1 (uridine diphosphate glucuronosyltransferase family 1 member A1).[5,38]

PIs are involved in clinically significant drug interactions. Atazanavir, darunavir and lopinavir are metabolized by CYP3A4.[10,12] Concomitant administration with agents that induce this enzyme (e.g. rifampin) are contraindicated. PIs are inhibitors of CYP3A4.[5,38] Particularly, ritonavir is a potent CYP3A4 inhibitor. It should be used with caution in combination with any CYP3A4 substrate.[41] Moreover, some PIs are substrates of the p-glycoprotein (pgp) efflux pump.[5]

The pharmacokinetic enhancers, such as cobicistat and ritonavir, are potent CYP3A4 inhibitors. They are usually combined with other ARV drugs (e.g. PIs or INSTI) that are CYP3A4 substrrates, in order to decrease the metabolism and increase the half-life of the concomitant agent. Both are involved in the majority of drug interactions associated with PIs.[12]

Table 3. Combination Products: Pharmacokinetics[9,10,42]

Combination Products containing NRTIs

Component of FDC, *trade name* and abbreviation	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Abacavir *Trizivir* (ABC/ZDV/3TC) *Epzicom* (ABC/3TC) *Triumeq* (ABC/3TC/DTG)	Rapid& Extensive BA: 83% Tmax: 0.7 to 1.7 hr	PB: 50% Vd: 0.86 L/kg	Hepatic: Extensive Alcohol dehydrogenase, glucuronyl transferase Carbovir triphosphate	Renal 81% Fecal 16%	Adult: 1.5 hr Age ≥3 months to ≤13 years: 1 to 1.5 hr Hepatic impairment: ↑ by 58%
Emtricitabine *Atripla* (FTC/EFV/TDF) *Complera* (FTC/RPV/TDF) *Descovy* (FTC/TAF) *Genvoya* (FTC/EVG/c/TAF) *Odefsey* (FTC/RPV/TAF) *Stribild* (FTC/EVG/c/TDF) *Truvada* (FTC/TDF)	Rapid & Extensive BA: • Capsule 93% • Solution 75% Tmax: 1 to 2 hours	PB: <4% Vd: 1.4 L/kg	Hepatic oxidation and glucuronic acid conjugation None	Renal 85% Fecal 14%	Adult: 10 hr
Lamivudine *Combivir* (3TC/ZDV) *Epzicom* (3TC/ABC) *Trizivir* (3TC/ZDV/ABC)	BA: 80 to 85% Tmax: • Adults: 1 to 1.l5 hr • Neonates: 2.5 hr	PB <36% Vd 1.3 L/kg	Minor None	Renal >70%	Adult: 5 to 7 hr Age 4 months to 14 years: 2 hr
Tenofovir Alafenamide *Descovy* (TAF/FTC) *Genvoya* (TAF/EVG/c/FTC) *Odefsey* (TAF/RPV/FTC)	BA: ↑ 65% with a high-fat meal Tmax: 0.48 hr	PB: 80% Vd: N/A	Intracellularly by carboxyesterase 1 CYP: minimal Tenofovir diphosphate Tenofovir	Fecal 37.1% Urine <1%	0.5 to 1 hr
Tenofovir Disoproxil Fumarate *Atripla* (TDF/EFV/FTC) *Complera* (TDF/RPV/FTC) *Stribild* (TDF/EVG/c/FTC)	BA: 25%, ↑ 40% with high-fat meal Tmax: • Adults: 1 hr • Age 2 to <16 years: 1.93 hr	PB: <7% to serum proteins Vd: 1.2 to 1.3 L/kg	Minimal Tenofovir diphosphate Tenofovir	Renal: • 32% unchanged (oral) • 70-80% unchanged (IV)	Oral: 17 hr IV: 4 to 8 hr

Component of FDC, *trade name* and abbreviation	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Truvada (TDF/FTC)					
Zidovudine *Combivir* (ZDV/3TC) *Trizivir* (ZDV/3TC/ABC)	Well absorbed BA: similar for tablets, capsules, syrup • Adults: 64% • Age <14 days: 89% • Age 14 days to 3 months: 61% • Age 3 months to 12 years: 65% Administer with or without food Tmax: 30-90 minutes	PB: 25% to 38% Vd: 1 to 2.2 L/kg	Hepatic glucuronidation None	Renal excretion: • Oral: 72-74% as metabolites; 14-18% as unchanged drug • IV: 45-60% as metabolites; 18-29% unchanged drug	Adult: 0.5 to 3 hr Age < 14 days: 3.1 hr Age 14 days to 3 months: 1.9 hr Age 3 months to 12 years: 1.5 hr
Combination Products containing INSTIs					
Dolutegravir *Triumeq* (DTG/ABC/3TC)	• Effects of food: Increased extent, decreased rate • Take 2 hours before or 6 hours after taking cation containing antacids or laxatives, sucralfate, oral supplements with iron or calcium, or buffered medications. Alternatively, take DTG with calcium or iron together with food. • Tmax: 2-3 hr	PB: 99%	Primarily: UGT1A1 Secondarily: CYP3A	Feces (53% as unchanged drug) Urine (31% as metabolites, <1% as unchanged-drug)	14 hr
Elvitegravir *Genvoya* (EVG/c/FTC/TAF) *Stribild* (EVG/c/FTC/TDF)	Tmax: 4 hr AUC increases with food	PB: 98-99%	Hepatic via CYP3A and glucuronidation by UGT1A1/3	Fecal: 94.8% unchanged Renal: 6.7% as metabolites	9 hr
Combination Products containing NNRTI					
Efavirenz *Atripla* (EFV/FTC/TDF)	Food increases BA. Administer on an empty stomach	PB > 99%	CYP3A and CYP2B6	Fecal: 16-61% unchanged Renal: 14-34% (inactive metabolites), <1% (unchanged drug)	52-76 hr (single dose) 40-55 hr (multiple doses)
Rilpivirine Odefsey (RPV/FTC/TAF) Compera (PRV/FTC/TDF)	Effect of food: increased systemic exposure	PB: 99%	CYP3A	Fecal: 85% (25% as unchanged drug) Renal: 6%	50 hr

Component of FDC, *trade name* and abbreviation	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
	BA reduced under fasting conditions and with a protein-rich nutritional drink				
Combination Products containing PIs					
Atazanavir *Evotaz* (ATV/c)	Rapidly absorbed, enhanced with food Tmax: 2-3 hr	PB: 86%	CYP3A4	Feces: 79%, 20% as unchanged drug Urine: 13%, 7% as unchanged drug	Unboosted therapy: 6.5-7.9 hr Boosted therapy with ritonavir: 9-18 hr
Darunavir *Prezcobix* (DRV/c)	BA: 82%, increased 30%-40% with food Tmax: 2.5-4 hr	PB: 95%	CYP3A4	Feces: 80% (41% as unchanged). Urine: 14% (8% as unchanged)	15 hr
Lopinavir *Kaletra* (LPV/r)	BA: low Tmax: 4 hr	PB: 98-99	CYP3A4	Feces: 83% (20% as unchanged drug) Urine: 10% (<3% as unchanged drug)	5-6 hr
Combination Products containing Pharmacokinetic Enhancers					
Ritonavir *Kaletra* (LPV/r)	BA: > 60%, increased with food Tmax: 2 hr (fasted), 4 hr (nonfasted)	PB: 98-99	CYP3A4 and CYP2D6	Urine: 11% (4% as unchanged) Feces: 86% (34% as unchanged)	3-5 hr Children: 2-4 hr
Cobicistat *Genvoya* (EVG/c/FTC/TAF) *Stribild* (EVG/c/FTC/TDF)	Tmax: 3.5 hr	PB: 97-98%	Hepatic: Extensive CYP3A4 (major) CYP2D6 (minor)	Feces: 86.2% Urine: 8.2%	3-4 hr

Key-to-Abbreviations: AUC=Area under the curve; BA=bioavailability; N/A=not available; PB=protein binding; Tmax=time to maximum serum concentration; Vd=volume of distribution; FDC= Fixed-dose combination

Special Populations

In general, the recommendations for initiation of ART and goals of therapy in adults and adolescents are the same for special populations with HIV infection. Individual patient characteristics should be considered before starting ART. Pharmacokinetics, drug interactions and safety profiles are considered in treatment decisions, and dosage adjustments may be required in some populations.[5]

Pregnant women should start ART as early as possible to prevent mother-to-child transmission of HIV infection. Pharmacokinetic changes during pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially for protease inhibitors. According to the CDC and DHHS recommendations, mothers should be instructed not to breastfeed due to the potential for HIV-1 transmission. During pregnancy, ABC in combination with 3TC or TDF plus FTC or 3TC are considered the preferred dual NRTI backbones for treatment naïve pregnant women.[29] Zidovudine in combination with lamivudine is now classified as an alternative backbone by U.S. guidelines due to the higher dosing frequency and the higher incidence of adverse effects compared to the preferred backbones.[29] TAF-containing regimens should be avoided for initial ART due to limited safety and pharmacokinetic information. Dolutegravir/TDF/FTC is a recommended regimen for non-pregnant adults; however it is not recommended for pregnant women due to the limited efficacy and safety information available.[29]

Older patients should receive ART as soon as possible, regardless of CD4 T-cell count, due to the increased risk of non-AIDS related complications and reduced response to ART in this patient population. Given that polypharmacy is frequent in older patients due to comorbidities, the potential for drug interactions is high and providers should regularly update the patients' medication profile and assess for drug interactions.[5]

ART is recommended in patients with HIV-coinfections, as the benefits of ART almost always outweigh the risks (drug-induced liver injury, drug-drug interactions, etc.). In patients with HIV and tuberculosis coinfection, both ART and tuberculosis treatments should be initiated immediately. All patients with an HIV/Hepatitis C virus coinfection, including those with cirrhosis, should receive ART, regardless of CD4, T-cell count. Patients with an HIV/Hepatitis B visrus coinfection should receive an ART regimen with an NRTI backbone including a fixed dose combination of TDF/FTC or TAF/FTC, or TDF plus 3TC, as all of them are active against both HIV and Hepatitis B virus infections.[5]

In pediatric patients, urgent initiation of ART is recommended in all children <12 months of age, regardless of clinical symptoms, immune status or viral load. In children ≥1 year, the urgency at which to initiate treatment depends on CDC stage and CD4, T-cell count.[24]

Patients with reduced kidney function may require a dosage adjustment. Tenofovir alafenamide plus emtricitabine can be used safely in patients with renal dysfunction. In patients with severe renal disease, tenofovir disoproxil fumarate should be avoided. The co-formulation abacavir, lamivudine and dolutegravir can be prescribed, unless patients have creatinine clearance <50 mL/min.[5]

Dosage modifications may be required based upon concomitant disease states. In patients with osteoporosis, TDF should be avoided due to its bone toxicity. Given that there is controversial information regarding the potential association between abacavir and cardiovascular disease, other ARV drugs are recommended in this type of patients. In patients with cardiovascular disease, tenofovir-containing regimens are a treatment option. Due to the risk of serious hypersensitivity reactions abacavir is contraindicated in patients who are positive for HLA-B*5701.

Table 4 describes the main recommendations for fixed dose combinations in special populations (patients with hepatic and renal impairment, pregnancy and lactation, pediatric and geriatric populations).

Table 4. Combination Products: Recommendations for Special Populations[9-11,29]

Combination Products containing NRTIs

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
Abacavir (ABC) *Trizivir* (ABC/ZDV/3TC) *Epzicom* (ABC/3TC) *Triumeq* (ABC/3TC/DTG)	Mild hepatic impairment: dose reduction required (200 mg BID, oral solution recommended) Moderate or severe hepatic impairment: contraindicated use	Not studied	Pregnancy: FDA Pregnancy Category (C) * Use adult dose * High placental transfer to fetus[b] * Animal studies: fetal malformations and other embryonic and fetal toxicities in rats at 35 times the human exposure at the recommended clinical dose * No evidence of human teratogenicity * Available human and animal data from APR suggest that **ABC does not increase the risk of major birth defects** overall compared with the background rate * ABC/3TC and TDF/FTC or TDF/3TC are considered preferred NRTI backbones in pregnant women by U.S. guidelines (ZDV/3TC is an alternative NRTI backbone) * Rate of hypersensitivity reactions in pregnancy is unknown. Testing for HLA-B*5701 is required before starting ABC Lactation: Excreted into breast milk **DHHS and CDC recommendation**: mothers should be instructed **not** to **breastfeed** due to the potential for HIV-1 transmission	Age ≥3 months (Dosing by body weight)	Adult dosing. Limited data. Caution should be exercised for dose selection due to an increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
Emtricitabine (FTC) *Atripla* (FTC/EFV/TDF) *Complera* (FTC/RPV/TDF) *Descovy* (FTC/TAF)	No dosage adjustment required	Dosage adjustment in patients with CrCl <50 mL/min or who require dialysis	Pregnancy: FDA pregnancy Category (B) * Use adult dose * High placental transfer to fetus[b] * Animal studies showed no increase in fetal variations or malformations. No adequate and well-controlled studies of FTC in pregnant women. No evidence of human teratogenicity * FTC can be used during pregnancy only if clearly necessary	Indicated in all pediatric groups	Caution should be exercised for dose selection due to an increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
Genvoya (FTC/EVG/c/TAF) *Odefsey* (FTC/RPV/TAF) *Stribild* (FTC/EVG/c/TDF) *Truvada* (FTC/TDF)			* ABC/3TC and TDF/FTC or TDF/3TC are considered preferred NRTI backbones in pregnant women by U.S. guidelines (ZDV/3TC is an alternative NRTI backbone) * If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped. Lactation: excreted into breast milk **DHHS and CDC Recommendation**: where formula is accessible, affordable, safe, and sustainable, and the risk of infant mortality due to diarrhea and respiratory infections is low, complete avoidance of breast-feeding by HIV-infected women is recommended to decrease potential transmission of HIV		disease or other drug therapy
Lamivudine (3TC) *Combivir* (3TC/ZDV) *Epzicom* (3TC/ABC) *Trizivir* (3TC/ZDV/ABC)	No dosage adjustment required. However, has not been studied in the setting of decompensated liver disease	Dosage adjustment in adults and adolescents (≥25 kg) based on CrCl	Pregnancy: FDA pregnancy Category (C) * Use adult dose * High placental transfer to fetus[b] * No evidence of human teratogenicity * Available evidence does not suggest that 3TC use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes * ABC/3TC and TDF/FTC or TDF/3TC are considered preferred NRTI backbones in pregnant women by U.S. guidelines (ZDV/3TC is an alternative NRTI backbone) * If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped Lactation: excreted into breast milk **DHHS and CDC recommendation**: mothers should be instructed **not** to **breastfeed** due to the potential for HIV-1 transmission	Age ≥3 months	Caution should be exercised for dose selection due to an increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
Tenofovir Alafenamide Fumarate (TAF)	No dosage adjustment required in patients with mild hepatic impairment (Child-Pugh A)	No dosage adjustment required in patients with	Pregnancy: * Insufficient data to make dosing recommendation	Age ≥18 years	Limited data. Caution should be exercised for dose selection

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
Descovy (TAF/FTC) *Genvoya* (TAF/EVG/c/FTC) *Odefsey* (TAF/RPV/FTC)	Not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment	mild, moderate or severe renal disease Not recommended in patients with CrCl<15 mL/min	* No available data on placental transfer of TAF * No evidence of teratogenicity in rats. Insufficient data to assess for teratogenicity in humans * Insufficient data to determine the risk for birth defects or miscarriage * Insufficient data to recommend TAF for initial therapy in antiretroviral-naive pregnant women. Administer TAF only if the potential benefit outweighs the potential risk to the fetus * Renal function should be monitored because of **potential for renal toxicity** Lactation: * It is not known if TAF is excreted in breast milk **DHHS and CDC Recommendation**: Mothers coinfected with HIV are discouraged from breastfeeding to decrease potential transmission of HIV		due to and increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
Tenofovir Disoproxil Fumarate (TDF) *Atripla* (TDF/EFV/FTC) *Complera* (TDF/RPV/FTC) *Stribild* (TDF/EVG/c/FTC) *Truvada* (TDF/FTC)	No dosage adjustment required	Dosage adjustment in patients with CrCl<50 mL/min or who require dialysis	Pregnancy: FDA pregnancy Category (B) * Use adult dose * High placental transfer to fetus * No evidence of human teratogenicity * Human studies demonstrate no effect on intrauterine growth, but data are conflicting about potential effects on growth outcomes later in infancy * ABC/3TC and TDF/FTC or TDF/3TC are considered preferred NRTI backbones in pregnant women by U.S. guidelines (ZDV/3TC is an alternative NRTI backbone) * If HBV-coinfected, it is possible that an HBV flare may occur if TDF is stopped * Renal function should be monitored because of **potential for renal toxicity**	Age ≥2 years	Limited data. Caution should be exercised for dose selection due to an increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
			Lactation: * TDF is excreted in breast milk **DHHS and CDC Recommendation**: where formula is accessible, affordable, safe, and sustainable, and the risk of infant mortality due to diarrhea and respiratory infections is low, complete avoidance of breast-feeding by HIV-infected women is recommended to decrease potential transmission of HIV		
Zidovudine (AZT, ZDV) *Combivir* (ZDV/3TC) *Trizivir* (ZDV/3TC/ABC)	Insufficient data. Frequent monitoring of hematologic toxicities is advised	Dosage adjustment in patients with CrCl<15 mL/min (severe renal disease)	Pregnancy: FDA pregnancy Category (C) * Use adult dose * High placental transfer to fetus * No evidence of human teratogenicity * ZDV/3TC is considered an alternative NRTI backbone by U.S. guidelines in pregnant women (ABC/3TC and TDF/FTC or TDF/3TC are considered preferred NRTI backbones) Lactation: * ZDV is excreted in breast milk **DHHS and CDC recommendation**: mothers should be instructed **not** to **breastfeed** due to the potential for HIV-1 transmission	Age 4 weeks (>4 kg) to <18 years	Limited data. Caution should be exercised for dose selection due to an increased frequency of reduced hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Combination Products containing INSTIs

Dolutegravir *Triumeq* (DTG/ABC/3TC)	• No dosing adjustment required for mild or moderate hepatic impairment (Child-Pugh Class A or B). Not recommended with severe hepatic impairment	No dose adjustment needed for renal impairment	• There is insufficient human data on the use of DTG during pregnancy to inform a drug associated risk of birth defects and miscarriage. No evidence of teratogenicity in mice, rats, or rabbits • Animal studies show drug excretion into milk Mother to Child Transmission Prevention Not recommended since data is limited to support the use of DTG during pregnancy	pediatric patients weighing ≥30kg	Adult dosing. Use with caution

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
Elvitegravir *Genvoya* (EVG/c/FTC/TAF) *Stribild* (EVG/c/FTC/TDF)	• Mild-to-moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment necessary. • Severe hepatic impairment (Child-Pugh class C): Use is not recommended (has not been studied).	No dosage adjustment necessary	Pregnancy: FDA pregnancy Category (B) Lactation: **DHHS and CDC Recommendation**: where formula is accessible, affordable, safe, and sustainable, and the risk of infant mortality due to diarrhea and respiratory infections is low, complete avoidance of breast-feeding by HIV-infected women is recommended to decrease potential transmission of HIV	Not recommended for patients less than 12 years of age or weighing less than 35 kg.	Adult dosing

Combination Products containing NNRTIs

Efavirenz *Atripla* (EFV/FTC/TDF)	• Not recommended with moderate or severe hepatic impairment. • No dose adjustment necessary for mild hepatic impairment.	Renal insufficiency dose adjustments have not been studied, however adjustment is not expected to be necessary	• Pregnancy Risk Category: D* • Fetal risk has been demonstrated; Avoid in 1st trimester • Excretion into human breast milk occurs Mother to Child Transmission Prevention Recommended as an alternative option, secondary to the preferred PI and INSTI-based regimens More recent large meta-analyses provided compelling evidence for the DHHS panel to lessen this concern of pregnancy risk. This is consistent with the WHO and British HIV guidelines which all suggest EFV therapy can be used throughout pregnancy.	pediatric patients older than 3 months weighing ≥ 3.5 kg	Adult dosing
Rilpivirine Odefsey (RPV/FTC/TAF) Compera (PRV/FTC/TDF)	No dose adjustment required for mild or moderate (Child-Pugh Class A or B) hepatic impairment. PKs haven't been evaluated for more severe hepatic impairment	No dose adjustment is required in patients with mild or moderate renal impairment. Use caution with severe renal impairment.	• Pregnancy Risk Category: B • Animal studies show drug excretion into milk • No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans Mother to Child Transmission Prevention • Recommended as an alternative option, secondary to the preferred PI and INSTI-based regimens. • Routine dosing adjustment in all women is not recommended for RPV during pregnancy. Individual patients should be closely monitored.	adolescent patients at least 12 years old	Not described

Combination Products containing PIs

Atazanavir *Evotaz* (ATV/c)	Dosage adjustment.	Mild to severe impairment: No dosage	• Low placental transfer to fetus • atazanavir does not increase the risk of major birth defects overall compared to the background rate	Infants ≥3 months, Children and	Adult dosing

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
	Severe hepatic impairment (Child-Pugh class C): Use is not recommended.	adjustment necessary.	• Must be given as lowdose RTV-boosted regimen in pregnancy Lactation: **DHHS and CDC recommendation**: mothers should be instructed not to breastfeed due to the potential for HIV-1 transmission	Adolescents <18 years	
Darunavir *Prezcobix* (DRV/c)	Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustments necessary Severe impairment (Child-Pugh class C): Use not recommended	no dosage adjustments	Pregnancy Category C: Darunavir should be used during pregnancy only if the potential benefit justifies the potential risk. • Low placental transfer to fetus • Must be given as lowdose, RTV-boosted regimen Lactation: **DHHS and CDC recommendation**: mothers should be instructed not to breastfeed due to the potential for HIV-1 transmission	pediatric patients 3 years of age and older	Adult dosing
Lopinavir *Kaletra* (LPV/r)	Use caution in hepatic impairment (metabolized primarily by the liver)	Not studied	• Low placental transfer to fetus • Lopinavit does not increase the risk of major birth defects overall compared to the background rate • Oral solution not recommended for use in pregnancy • LPV/r QD not recommended	pediatric patients (14 days and older)	Use with caution

Combination Products containing Pharmacokinetic Enhancers

Ritonavir *Kaletra* (LPV/r)	Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary Severe impairment: Not recommended (not studied)	Not studied	• Low placental transfer to fetus • Lopinavit does not increase the risk of major birth defects overall compared to the background rate • Oral solution not recommended for use in pregnancy • LPV/r QD not recommended Lactation: **DHHS and CDC recommendation** recommendation: mothers should be instructed not to breastfeed due to the potential for HIV-1 transmission	Infants >1 month and children, adolescents	Adult dosing

Active Substance and Combination Products	Hepatic impairment	Renal Impairment	Pregnancy and Lactation	Pediatric	Geriatric
Cobicistat *Genvoya* (EVG/c/FTC/TAF) *Stribild* (EVG/c/FTC/TDF)	No dosage adjustment necessary	When not used with concomitant TDF: No dosage adjustment necessary. When used with concomitant TDF: CrCl ≥70 mL/min: No dosage adjustment necessary. CrCl <70 mL/min: Use is not recommended.	• No data on placental transfer of COBI are available. • Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Lactation: **DHHS and CDC recommendation**: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV	≥18 years	Adult dosing

Key Abbreviations ART=antiretroviral therapy, cART= combination antiretroviral therapy, AE= Adverse Events, APR= Antiretroviral Pregnancy Registry, CDC= Center for Disease Control and Prevention; CrCl= creatinine clearance; DHHS: Department of Health and Human Services

Methods

Literature Search

Search strategies were developed by an Informational Scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. Two methodological filters were used, one for systematic reviews, another for randomized controlled trials. Results were limited to English language. Databases were searched from date of inception forward. Searches were conducted in January and February 2017. We screened the reference lists of related systematic reviews. Moreover, we also searched:

1. National Institute of Health (NIH), Centers for Disease Control and Prevention, World Health Organization, International Antiviral Society-USA Panel and European AIDS Clinical Society web-sites for the most recent HIV treatment guidelines.
2. Food and Drug Administration (Drugs@FDA: FDA Approved Drug Products: https://www.accessdata.fda.gov/scripts/cder/daf/) for prescribing information package inserts
3. Evidence based drug information databases (Micromedex, Lexicomp, Epocrates and UpToDate)

Complete search strategies and terms are available in Appendix B.

Screening

At least two review authors screened titles and abstracts. The full text for all citations receiving two inclusion votes was retrieved; screening and inclusion were determined by the lead author. Opposing screening votes were resolved through discussion between reviewers or a third person. The PRISMA flow chart[43] for the review process is shown in Figure 1.

Criteria for including systematic reviews and studies in this report

Systematic reviews and randomized controlled trials (RCTs) providing data on head-to-head efficacy comparisons between combination products were included. For drugs/comparisons where a systematic review (or reviews) provided robust data, we examined only those trials published after the search date(s) of the systematic review(s). In some cases, data from the main RCTs of interest included in the systematic review were extracted. For comparisons with no systematic review data, we examined data from multiple RCTs.

Systematic reviews and RCTs were included in the analysis if they met the following eligibility criteria:

- They had to evaluate intra-class, head-to-head efficacy drug comparisons for the treatment of HIV-1 among the two drug classes reviewed: 1) Nucleoside/nucleotide reverse transcriptase inhibitors, as part of a triple ARV regimen, and 2) Fixed dose combinations, as single tablet regimens or as part of a triple ARV regimen

- They had to include HIV-1 infected treatment naïve patients
- The primary endpoint had to be related to clinical efficacy (i.e. virological outcome endpoints, clinical progression of disease, mortality outcomes, etc.) and had to be measured out to at least 48-weeks.

Studies were excluded if they met the following exclusion criteria:

- Studies evaluating non-FDA-approved indications such as HIV transmission prevention, post-exposure prophylaxis, or HIV-2
- Studies containing monotherapy or dual therapy treatment arms
- Studies in HIV-infected treatment experienced patients
- Studies measuring safety as primary outcome
- Other type of studies (e.g. non-comparative or non-randomized trials, placebo-controlled studies, phase 2 studies, observational studies, in vitro studies, animal studies, cost-effectiveness studies, etc.)

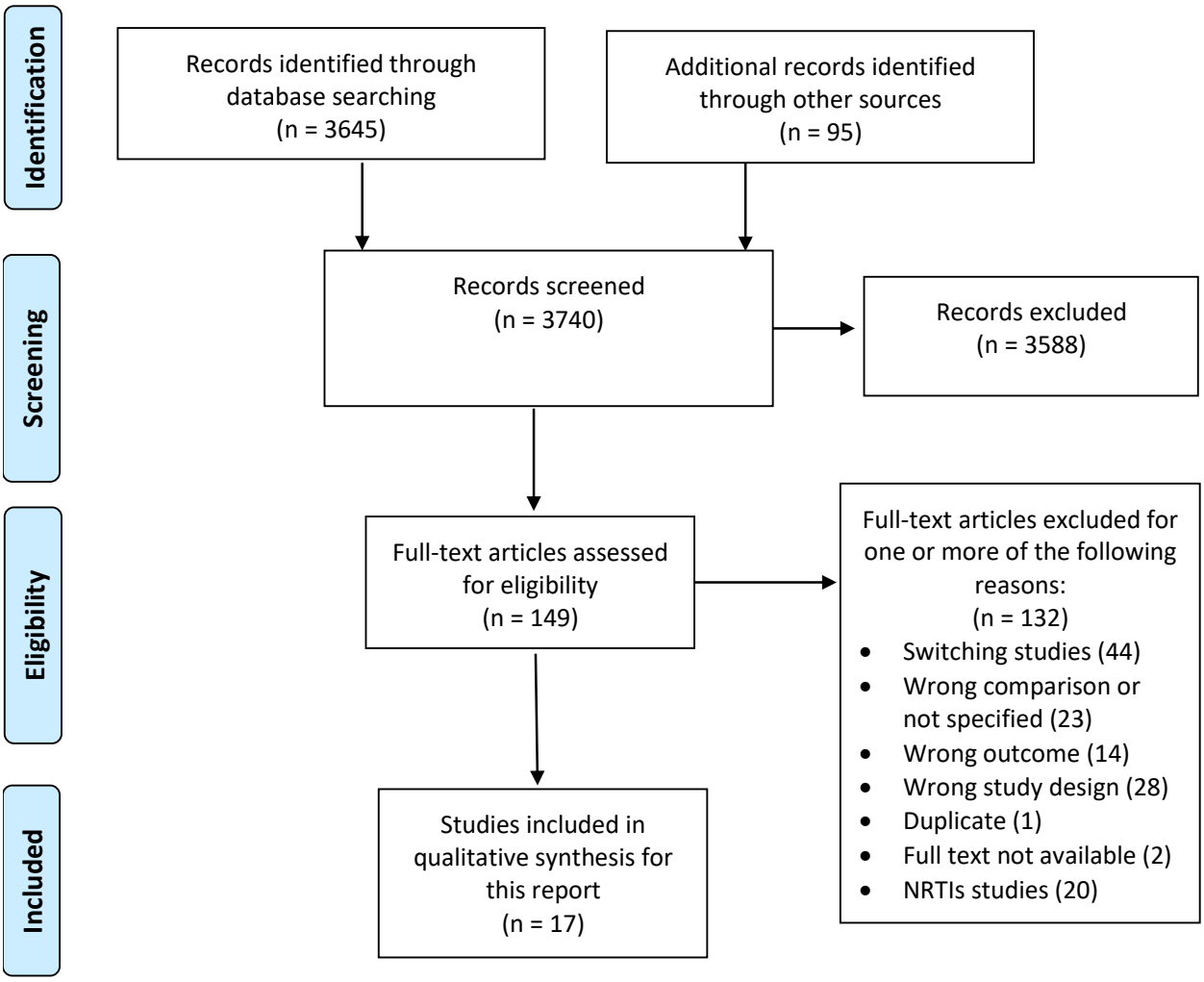

Figure 1. PRISMA Flow Diagram of the selection process

Clinical Efficacy and Safety

Clinical evidence involving head-to-head fixed dose combination (FDC) comparisons is presented for those FDCs currently available in the United States. Figure 1 shows the study selection process. From a total of 3,740 records identified using the developed search strategy, we included 17 references, of which four were systematic reviews/meta-analyses and nine were randomized controlled trials (RCTs). A single RCT may be described in several references. A list containing the excluded references is provided in Appendix D.

Among the fourteen FDC ART medications available in the U.S., only eight were studied in at least one comparative clinical trial. No head-to-head comparisons for initial HIV treatment were identified for the most newly approved combination products FTC/RPV/TAF (Odefsey) and FTC/TAF (Descovy), which were approved by the FDA in April 2016 and March 2016, respectively. Evidence is also lacking for ATV/c (Evotaz), DRV/c (Prezcobix), ABC/3TC/ZDV (Trizivir) and LPV/r (Kaletra). Some trials have suggested less efficacy for Trizivir compared to NNRT-based regimens[44], and therefore it is not recommended by U.S. guidelines. LPV/r together with 2 NRTIs is no longer recommended for initial therapy due to the availability of other PIs with better safety profiles and less dosing frequency. These may be potential reasons explaining the lack of head-to-head comparisons.

Overall, the most common primary endpoint measured throughout the included studies was virological suppression at week 48, defined as the percentage of patients achieving plasma HIV-1 RNA ≤50 copies/mL. The main secondary endpoints include immunological recovery, virological failure with resistance, adherence to ART, and safety outcomes. Appendix C outlines the design and the main efficacy and safety results of the most relevant studies considered for the evaluation.

TAF/EVG/c/FTC single-tablet regimen compared to TDF/EVG/c/FTC single-tablet regimen

The efficacy and safety of TAF/EVG/c/FTC (Genvoya) has been compared to TDF/EVG/c/FTC (Stribild) in one meta-analysis and two randomized controlled trials (Studies GS-US-292-0104 and GS-US-292-0111):

- **Wang et al** (2016)[45] performed a meta-analysis of 6 RCTs to investigate the efficacy and safety of tenofovir alafenamide in comparison to tenofovir disoproxil fumarate, both as part of antiretroviral FDCs containing elvitegravir, cobicistat and emtricitabine. A total of 5,888 treatment naïve and treatment experienced HIV-1 adult patients were included. Only data from the subgroup of treatment naïve patients is presented (4 RCTs, n=3,790) in this report. Both efficacy endpoints, the viral suppression (HIV-1 RNA <50 copies/mL) at week 48 and the virologic failure with resistance, were reported to be similar between treatment groups, relative risk (RR) 1.01, 95%CI (0.99 to 1.04) and RR 1.08, 95% CI (0.52 to 2.24), respectively. Although this report only includes an evaluation of HIV combination products in treatment-naïve patients, it should be highlighted that the virologic suppression

rate was significantly higher in patients switching from TDF combinations to TAF than those continuing the previous TDF combination. Regarding safety outcomes, no differences were observed with respect to the overall adverse event rate or laboratory abnormalities. However, the TAF group had statistically significant better renal safety profile, less bone mineral density reduction at spine and hip from baseline, and no discontinuation due to renal adverse events in comparison to TDF group. Mean changes in total and HDL cholesterol from baseline were significantly higher in the TAF group as compared to TDF group.

- **Sax et al** (2015)[46] and **Wohl et al** (2016)[47] evaluated the efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat and emtricitabine, in two clinical controlled, double-blind, non-inferiority trials (Study GS-US-292-0104 and GS-US-292-0111) through week 48 and 96. These studies (performed at different sites) were included in the meta-analysis described above[45], but data was extracted from each trial since they were considered relevant for this report. Both trials included 1,733 patients from 178 outpatient centers in 16 countries. At week 48, the single-tablet regimen containing TAF was noninferior to the single-tablet containing TDF with respect to the percentage of patients that achieved HIV-1 RNA <50 copies/mL (92% vs. 90%, respectively; adjusted difference 2.0%, 95% CI –0.7 to 4.7%). Both co-formulations were well tolerated and discontinuations due to adverse events were infrequent. Notably, the TAF treatment resulted in a more favorable renal and bone safety profile compared to TDF group. A lower reduction in bone mineral density at lumbar spine and hip was found among the TAF arm versus TDF arm. Moreover, changes in some renal parameters such as estimated glomerular filtration rate, serum creatinine and proteinuria were smaller in the TAF arm versus TDF arm. Statistically significant greater increases in lipid parameters (triglycerides levels, total, LDL and HDL cholesterol levels) were observed in the TAF group compared to TDF group.
  At week 96, the virological suppression rate in the TAF group continued to be noninferior to the TDF group. Long-term renal and bone effects remained lower in TAF patients compared to TDF. According to the authors' opinion, the favorable effects observed with TAF could be related to the lower tenofovir plasma levels reported in patients treated with TAF-containing regimens[48]. The favorable lipid profile for the TDF group was consistent with week 48 results.

Overall, both the meta-analysis and the clinical trial results identified that TAF/EVG/c/FTC was similar to TDF/EVG/c/FTC in terms of virological suppression. Evidence indicated a more favorable renal and bone safety profile for TAF/EVG/c/FTC compared to TDF/EVG/c/FTC, while negative effects on some lipid parameters were observed in TAF/EVG/c/FTC versus TDF/EVG/c/FTC. Long-term data showed similar efficacy and safety trends.

TDF/EVG/c/FTC single-tablet regimen compared to EFV/FTC/TDF single-tablet regimen

The efficacy and safety of TDF/EVG/c/FTC (Stribild) has been compared to EFV/FTC/TDF (Atripla) in a non-inferiority, randomized, controlled trial (Study GS-US-236-0102) described by **Sax et al** (week 48 results),[49] **Zolopa et al** (week 96 results),[50] and **Wohl et al** (week 144 results).[51] A total of 700 adult patients with HIV infection were included. At week 48, TDF/EVG/c/FTC was noninferior to EFV/FTC/TDF in terms of virological suppression (proportion of patients with HIV RNA <50 copies/mL: 87.6% vs 84.1%, difference 3.6%, 95% CI –1.6% to 8.8%; non-inferiority margin= 12%). Similarly, there were no differences in response by subgroup of patients. The immunological response was significantly higher in TDF/EVG/c/FTC arm at week 48. Generally, discontinuations due to adverse events were low and similar between groups. The incidence of neuropsychiatric (i.e. insomnia, abnormal dreams, dizziness) adverse events and rash were more frequently reported with EFV/FTC/TDF, which is not unexpected for efavirenz-based regimens. Nausea was more common with EVG/c/FTC/TDF. The incidence of increased serum creatinine and decrease in glomerular filtration rate was significantly higher in the EVG/c/FTC/TDF arm compared to the EFV/FTC/TDF arm, and may be associated with cobicistat and tenofoviv disoproxil fumarate. Less than 5% of patients discontinued the study product due to adverse events including renal, neuropsychiatric and nausea adverse events. A more favorable lipid profile was observed in the EVG/c/FTC/TDF group compared to the EFV/FTC/TDF group.

At week 96 and week 144, durable and comparable virological suppression was demonstrated for both products (EVG/c/FTC/TDF vs. EFV/FTC/TDF: 84% vs 82% at week 96 and 80.2% vs 75.3% at week 144). The development of resistance to one or more components was infrequent. The long-term safety profile was consistent with the week 48 results and was characterized by no new or unexpected adverse events and by infrequent discontinuations due to adverse events. Two patients discontinued therapy due to adverse renal events at week 96 and one due to an increase in creatinine at week 144 in EVG/c/FTC/TDF arm compared to none in EFV/FTC/TDF arm. As observed at week 48, a favorable safety profile concerning neuropsychiatric and rash events was detected in the EVG/c/FTC/TDF group compared to EFV/FTC/TDF through week 144.

In summary, study GS-US-236-0102 suggested that TDF/EVG/c/FTC is non-inferior to EFV/FTC/TDF through week 144. A favorable safety profile concerning neuropsychiatric, rash and lipid change events was detected in EVG/c/FTC/TDF group compared to EFV/FTC/TDF through week 144. Nevertheless, an unfavorable safety profile regarding renal adverse events was observed for the EVG/c/FTC/TDF group versus EFV/FTC/TDF group.

RPV/FTC/TDF single-tablet regimen compared to EFV/FTC/TDF single-tablet regimen

Cohen et al (2014)[52] and **Van Lunzen et al** (2016)[53] conducted a phase 3, 96-week, randomized, open-label, international, non-inferiority trial to evaluate the comparative efficacy and safety of RPV/FTC/TDF (Complera) versus EFV/FTC/TDF (Atripla) [STaR study]. Results

from this study demonstrated the RPV combination to be non-inferior to the EFV combination at week 48 and 96 with respect to viral response (week 96: RPV 78.8% vs. EFV 71.2%; difference 7.2%, 95% CI -1.1–13.4%). Moreover, superiority was demonstrated at week 96 for the subgroup of patients receiving RPV/FTC/TDF with baseline HIV RNA ≤100,000 copies/mL and CD4 baseline >200 cells/µl in comparison to the EFV group. Nonetheless, the RPV group was noninferior to the EFV group for the subgroup of patients with baseline HIV RNA >100,000 copies/mL and baseline HIV RNA 100,000-500,000 copies/mL. Non-inferiority was not achieved in the subgroup of patients with a baseline HIV RNA>500,000 copies/mL or in those with baseline CD4 <200 cells/µl. With respect to drug resistance, the subgroup with viral load >100,000 copies/mL at baseline reported a higher rate of virologic failure due to resistance in the RPV arm compared to EFV arm. Superior safety and tolerability was reported in the RRV group in comparison to EFV group at week 96. For the RPV group, lower incidences of neuropsychiatric adverse events, rash, and adverse-effect related discontinuations were reported compared to the EFV group. A decreased in glomerular filtration rate was observed in the RPV group compared to EFV. No proximal renal tubulopathy was identified in either group.

RPV/FTC/TDF was noninferior compared to EFV/FTC/TDF in the overall population at week 96 with respect to virological suppression, and was superior in certain subgroups (patients with baseline HIV RNA ≤100,000 copies/mL and CD4 baseline >200 cells/µl). The study demostrated an improved safety profile for the RPV group compared to the EFV group. Moreover, in the subgroup with viral load >100,000 copies/mL at baseline, the RPV arm revealed a higher risk of virologic failure due to resistance compared to the EFV arm.

Single-tablet containing DTG + ABC/3TC compared to EFV/FTC/TDF single-tablet regimen

The efficacy and safety of DTG plus ABC/3TC (future Triumeq) has been compared to EFV/FTC/TDF (Atripla) in one meta-analysis and one randomized controlled trial:

- **Rutherford et al** (2016)[54] conducted a systematic review of two randomized controlled trials including 833 HIV-infected adult patients. One of the studies was excluded for this evaluation since it was a phase 2 study. Only the meta-analysis results from the non-inferiority phase 3 trial at week 96 and 144 (SINGLE study) was considered in this report. With respect to efficacy, DTG in combination with the single-tablet containing ABC/3TC appeared to be superior to EFV/FTC/TDF in terms of viral suppression to non-detectable levels (less than 50 copies/mL) at week 144 (RR = 1.13, 95%CI 1.02 to 1.24). A higher increase in CD4 cell count at week 144 was observed in the DTG arm compared to the EFV arm. With respect to safety, a significantly lower proportion of patients discontinued treatment due to adverse events or death in the DTG group in comparison to EFV group at both week 96 and 144.

- The SINGLE study described by **Walmsley et al**[55,56] evaluates the efficacy and safety of DTG plus ABC/3TC versus EFV/FTC/TDF at week 48, 96 and 144. The primary efficacy endpoint (i.e. proportion HIV RNA less than 50 c/mL) at week 48 revealed that DTG plus

ABC/3TC was non-inferior to EFV/FTC/TDF (88% versus 81%; adjusted difference +7.4%, 95% CI 2.5%-12.3, non-inferiority margin=10%). Furthermore, a pre-especfied superiority analysis demonstrated a superior efficacy of DTG combination over the EFV regimen (p= 0.003). Statistically significant results were also observed for the secondary endpoints (i.e. time to viral suppression and immunological recovery) and no antiviral resistance was detected in the DTG group compared to 5 cases in the EFV arm. Regarding safety at week 48, the DTG group reported a lower incidence of serious adverse events and discontinuations due to adverse events. Rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were more common in the EFV arm, with the exception of insomnia that was more frequent in the DTG arm. At week 96 and 144, long-term virological response and safety results are consistent with those observed at week 48.

This SINGLE study together with a bioequivalence study of the fixed-dose combination of ABC, DTG and 3TC versus DTG plus ABC/3TC led to the U.S. approval of DTG/ABC/3TC (Triumeq).

Overall, both the meta-analysis and the SINGLE study arrived at the same efficacy and safety conclusions. Superior efficacy interms of virological suppression and fewer discontinuations due to adverse events were seen with DTG plus ABC/3TC compared to EFV/FTC/TDF through week 144.

Single-tablet containing TDF/FTC compared to single tablet containing 3TC/ZDV

The efficacy and safety of TDF/FTC (Truvada) has been compared to 3TC/ZDV (Combivir) in two noninferiority randomized controlled trials:

- Results from week 144 of Study 934 were reported by **Arribas et al**[57]. Data from week 48[33] and 96[34] were not considered in this report as one of the treatment groups did not receive a fixed-dose combination but the ARV drugs, separately. At week 96, both groups of patients shifted to receive dual FDC (TDF/FTC or ZDV/3TC) plus EFV and results at week 144 are reflected in Appendix C. Results from the primary efficacy endpoint did not differ between groups, although a greater virological suppression in the TDF/FTC group versus the ZDV/3TC group was reported (71% vs. 58%, respectively; p=0.004). No discontinuations due to adverse renal events were observed in any group. Nonetheless, a greater increase in limb fat and lipid parameters was observed in ZDV/3TC compared to TDF/FTC.

- **Campbell et al** (2012)[58] conducted a non-inferiority, phase 4, parallel assignment and open label trial comparing three fixed-dose combinations [PEARLS study]. Only results from TDF/FTC (Truvada) plus EFV versus 3TC/ZDV (Combivir) plus EFV were extracted as of interest for this report. The third combination regimen studied in this trial was not contain an FDA approved single tablet product.

The primary efficacy analysis consisted of a composite endpoint (i.e. disease progression, virologic failure or time to first occurrence of death). Efficacy results at 184 weeks (median) demonstrated no differences between groups treatment failures (18.0% in TDF/FTC vs 18.8% in 3TC/ZDV; HR 0.95, 95% CI 0.72-1.27, p=0.74). Similarly, no differences were observed in terms of immunological failure. With respect to safety, a composite primary endpoint including time till grade ≥3 sign/symptom, time till grade ≥3 laboratory abnormality, or time till treatment modification was used to measure safety events. TDF/FTC group demonstrated statistically significant better overall safety with less laboratory adverse events (46% in TDF/FTC arm vs 60% in 3TC/ZDV arm; HR 0.64, CI 0.54-0.76; p<0.001). In addition, superior safety was identified in the subgroup of women compared to men.

In summary, TDF/FTC was compared to ZDV/3TC, both in combination with EFV in two clinical trials. Noninferiority was demonstrated, although one trial noticed a significant greater virological suppression in TDF/FTC versus ZDV/3TC. It is of note that primary endpoints differed between trials. In relation to safety, a more favorable safety profile was observed in the TDF/FTC arm compared to ZDV/3TC arm.

Single-tablet containing TDF/FTC compared to Single-tablet containing ABC/3TC

Two meta-analysis and two randomized controlled trials comparing the efficacy and safety of TDF/FTC (Truvada) versus ABC/3TC (Epzicom) were considered for this report:

- **Hemkens et al** (2015)[59] performed a systematic review and meta-analysis of 22 RCTs comparing TDF versus non-TDF regimens (16 RTCs) and TDF/FTC versus ABC/3TC (6 RCTs) in combination with a third ARV agent. Data from the 6 RCTs was of interest, and therefore included in this report for evaluation. When analyzing the efficacy endpoint at week 48 (i.e. mortality, AIDS, fractures, virological failure and CD4 cell count), authors did not observe any significant difference between TDF/FTC and ABC/3TC groups. With respect to safety, a favorable effect on lipid parameters was identified in patients receiving with TDF/FTC at week 48. Conversely, statistically significant greater reductions in bone mineral density and glomerular filtration rate were observed in the TDF/FTC compared to the ABC/3TC arm.
- **Cruciani et al** (2014)[60] performed a systematic review and meta-analysis involving 30 RCTs conducted from 1996 to 2013. Only results from 6 RCTs that directly compare TDF/FTC versus ABC/3TC in combination with a third ARV agent were included in this report. The primary endpoint, defined as the proportion of subjects with HIV RNA <50 copies/mL, found no differences between treatment groups at week 48 or week 96. Likewise, similar results were seen irrespective of the baseline viral load at the same time points. Discontinuation rates secondary to adverse events revealed no differences between groups.

- ACTG A5202 was a phase 3, parallel assignment, blinded equivalence study described by **Sax et al** (2011)[61]. In this study, TDF/FTC was compared to ABC/3TC plus efavirenz or atazanavir/ritonavir. The efficacy and safety results were analyzed by stratifying the third ARV agent and by baseline HIV RNA. In the low HIV RNA stratum (<100,000 copies/mL at baseline), the first primary endpoint (i.e. time to virologic failure) was similar between both treatment groups regardless of the third ARV agent. The second primary endpoint (i.e. time until first regimen modification) was shorter for ABC/3TC compared to TDF/FTC with both EFV and ATV/r. Regarding the secondary endpoint, no difference was observed between groups with the exception of the time to regimen failure that was shorter for ABC/3TC compared to TDF/FTC when combined with ATV/r. The high HIV-RNA stratum reported a more rapid time to virologic failure in ABC/3TC plus ATV/r or EFV. The authors suggested that this result may reflect the high rate of mutations in the ABC/3TC with EFV group. In relation to safety, the time to the first safety event (primary safety endpoint) was shorter for ABC/3TC with EFV. When the backbones were combined with ATV/r, no differences were observed. At week 48 and 96, greater changes from baseline in lipid parameters were reported in patients receiving ABC/3TC with ATV/r and EFV. A decrease in creatinine clearance was observed in TDF/FTC with ATV/r group at both week 48 and 96. High adherence to ART was reported in both groups regardless of the third ARV agent.

- The HEAT study was a noninferiority trial where patients were randomized to receive a once-daily regimen of either ABC/3TC 600 mg/300mg or TDF/FTC 300 mg/200 mg, both with lopinavir/ritonavir 800 mg/200 mg. The results were presented by **Smith et al** (2009)[62] and demonstrated the non-inferiority of ABC/3TC to TDF/FTC at week 48 and week 96 (proportion of patients with HIV-1 RNA <50 copies/mL at week 48: 68% in ABC/3TC arm vs. 67% in TDF/FTC arm; 95%CI -6.63 to 7.40, p=0.913; noninferiority margin = -12%). Similar efficacy between groups were observed when subgroup analysis was performed by baseline viral load. Likewise, similar CD4 cell count increases and virologic failures were identified between groups through 96 weeks. Overall, both backbones seemed to be well tolerated with a global incidence of adverse events and a discontinuation rate due to AEs comparable between both groups. Nonetheless, TDF/FTC presented a less favorable renal safety profile compared to ABC/3TC with two discontinuations due to acute renal failure and 11 patients progressing to stage 3 chronic kidney disease. Cardiovascular adverse events were rare and none was related to the study drug. Lipid abnormalities appeared with more frequency in ABC/3TC arm compared to TDF arm.

Overall, the two meta-analyses and the HEAT study demonstrated noninferiority of ABC/3TC versus TDF/FTC in terms of the proportion of patients achieving HIV-1-RNA levels <50 copies/mL. Nevertheless, A5202 study considered a different primary efficacy endpoints (i.e time to virologic failure) and obtained different results in the two baseline HIV RNA stratums. In

the low HIV-RNA stratum no difference was observed in the time to virologic failure in any group; however, in the high HIV-RNA stratum a faster time to virologic failure was identified in ABC/3TC versus TDF/FTC with ATV/r or EFV. With respect to safety, a more favorable lipid profile was observed in TDF/FTC compared to ABC/3TC, whereas some studies reported more adverse renal events and greater bone mineral density reduction in TDF/FTC group compared to ABC/3TC group.

Safety

The safety profile of fixed dose combinations is characterized by the combination of the adverse events specific to each component. The most common adverse events caused by NRTIs include anemia, cardiomyopathy, lipid abnormalities, gastrointestinal distress, drug-induced hypersensitivity, skin rash, myopathy, nephrotoxicity, pancreatitis, peripheral neuropathy, hepatic steatosis with or without lactic acidosis, and lipodystrophy.[9-12] One of the most serious adverse event reported with NRTIs is potentially life-threatening mitochondrial toxicity,[12,63] clinically manifested by myopathy, peripheral neuropathy, pancreatitis, hepatic steatosis with lactic acidosis, and lipoatrophy.[41] A Black Box warning describing the potential risk of lactic acidosis is reflected in the prescribing information for all NRTI agents. Nevertheless, the most recently approved NRTIs, including abacavir, lamivudine, tenofovir disoproxil fumarate, tenofovir alafenamide and emtricitabine exhibit a lower risk of mitochondrial toxicity compared to the older NRTI agents (highest risk with didanosine and stavudine, followed by zidovudine).[12,41] Due to this high mitochondrial toxicity risk, didanosine and stavudine are rarely prescribed as ARV drugs for HIV treatment and are not recommended in any HIV treatment regimen according to the U.S. Department of Health treatment guidelines.[9,63]

Abacavir has been associated with hypersensitivity reactions,[64] a serious adverse event reported in less than 5% of patients[65] possessing the HLA-B*5701 gene allele. In order to minimize the risk, a HLA-B*5701 screening test is recommended in all patients before starting a treatment containing abacavir.[5] Moreover, abacavir has been linked to an increased risk of cardiovascular events. Islam et al[66] performed a meta-analysis showing greater cardiovascular risk in patients treated with abacavir compared to treatment naïve individuals with HIV (RR 1.80, 95% CI 1.43, 2.26; $p < 0.001$). By contrast, the meta-analysis described by Cruciani et al[67] did not reveal an association between abacavir and cardiovascular risk, including myocardial infarction. Hence, it is unclear whether abacavir may increase the risk of cardiovascular events.

Emtricitabine is generally well-tolerated and is one of the components of the preferred HIV regimen options, typically co-formulated with tenofovir or in triple combinations.[5] This NRTI is linked to hyperpigmentation of the palm and sole, headache, gastrointestinal disorders, skin rash and increased cough.[10,68]

Lamivudine is usually co-formulated with abacavir or in a triple combination with abacavir and dolutegravir.[5] Patients receiving lamivudine have reported headache, nausea, fatigue, nasal signs and symptoms, cough, neutropenia and elevation of transaminases as common adverse events (incidence > 10%).[41,69]

Patients treated with zidovudine have reported myopathy and severe hematologic abnormalities caused by bone narrow toxicity such as anemia, neutropenia and siderosis.[10,12,41,70] In a pediatric study conducted by Mulenga et al[71] that compares ABC, ZDV and d4T in combination with other ARV agents, more patients in the ZDV group reported anemia and neutropenia and required drug discontinuation compared with the other treatment arms. In

addition, a meta-analysis of six trials reported a greater negative impact on hematologic parameters in ZDV-containing regimens than in d4T-containing regimens.[72]

Treatment with tenofovir disoproxil fumarate has shown renal toxicity (proximal tubular dysfunction and decreased glomerular filtration rate), bone mineral density reduction, and hypercholesterolemia,[10,41,63,73] associated with high plasma levels of tenofovir. One systematic review[45] and two clinical trials including GS-US-292-0104 and GS-US-292-0111[46,47] described the efficacy and safety profile of two fixed-dose combinations containing TDF or TAF plus elvitegravir, cobicistat and emtricitabine in treatment naïve patients. Similar virologic suppression rates and comparable drug-related adverse events and drug discontinuations were reported between groups. Conversely, higher discontinuation rates due to renal events are reported with TDF regimens compared to TAF regimens, including reductions in glomerular filtration rate, increases in proteinuria markers and changes in proximal tubular function. Regarding bone toxicity, bone mineral density at lumbar spine and hip was significantly lower in the TDF group; although fracture rates were rare and similar between groups. With respect to lipid abnormalities, total cholesterol, triglycerides, LDL and HDL cholesterol appeared to be higher with TAF therapy compared to TDF; however the total cholesterol-to-HDL ratio was similar between groups.[73]

ACTG Study A5224s[74,75] and ASSERT[76-78] are trials that primarily analyzed the incidence of specific adverse events (i.e. lipoatrophy, bone mineral density and renal events) at week 96 in two co-formulations: ABC/3TC and TDF/FTC plus ATV/r or EFV. The ACTG Study A5224s[74] demonstrated that both groups similarly increased limb and visceral fat deposits.[74] In addition, data suggested that patients on ATV/r-containing regimens were prone to have greater increases in peripheral and central fat than EFV-containing regimens. Regarding the occurrence of bone adverse events,[75] this study revealed that ABC/3TC and TDF/FTC groups produced similar decreases in bone mineral density at the spine and hip; whereas a pronounced bone loss was observed when TDF/FTC was combined with ATV/r in comparison with the rest of groups.

The ASSERT study compares the safety profiles of ABC/3TC and TDF/FTC, both in combination with EFV[76-78]. At week 48, glomerular filtration rates were similar between groups but increases in markers of tubular dysfunction were significantly higher in the TDF/FTC group. Similarly, prominent increases in bone turnover markers and decreases in bone mineral density at the spine and hip were noted in TDF/FTC group compared to ABC/3TC group. At week 96, long-term renal and bone safety profiles were similar to that observed at week 48, favoring ABC/3TC.

Finally, tenofovir alafenamide is the most recent NRTI receiving FDA approval and is available as part of three coformulations for the treatment of HIV infection. These TAF combinations offer some pharmacokinetic and safety advantages in comparison to TDF combinations. Firstly, TAF is a prodrug that can achieve higher concentrations of the active form and lower tenofovir plasma exposure with the administration of lower oral doses than TDF.[46,48,79]

Secondly, TAF appears to have a more favorable renal and bone safety profile in comparison to TDF-containing regimens.[45-47,73,79] However, increases in lipid parameters were identified with TAF.[73]

The NNRTIs available in a single pill are efavirenz and rilpivirine. The most frequently reported adverse events with efavirenz are central nervous system toxicity such as dizziness, and insomnia, rash, gastrointestinal disorders, hyperlipidemia, and elevated hepatic transaminases.[10,12] Rilpivirine shares similar adverse effects with efavirenz, although no gastrointestinal disturbances have been reported with rilpivirne.[10]

Regarding the integrase inhibitors (INSTIs), dolutegravir and elvitegravir are avalilable in FDCs and are considered the preferred third agent for treatment-naïve patients according to the current US guidelines.[5,23] The most common adverse events of moderate to severe intensity related to dolutegravir use are adverse central nervous system events such as insomnia and headache, hyperglycemia, and changes in hepatic parameters.[10] Elvitegravir treatment is commonly associated with hypercholesterolemia, hyperglycemia, diarrhea and nausea.

With regards to protease inhibitors such as atazanavir, darunavir, lopinavir and ritonavir, the most common adverse events vary between the agents and include gastrointestinal disorders (i.e. diarrhea, nausea, vomiting), skin reactions and metabolic disturbances (e.g. hyperglycemia and hyperlipidemia).[12] Atazanavir is associated with hyperbilirubinemia, rash, and cough.[10] Skin reactions including Stevens-Johnson Syndrome have been reported in some cases with darunavir use. Hepatotoxicity has been reported and hepatic function should be monitored prior to and during darunavir therapy.[10] Lopinavir in combination with ritonavir produces gastrointestinal and neurologic adverse effects.[41] As with other PIs, the most common adverse events associated with ritonavir are asthenia, arthralgia, cough and gastrointestinal disorders such as nausea, vomiting, diarrhea, anorexia, abdominal pain and taste perversion.[10] . LPV/r together with 2 NRTIs is no longer recommended for initial therapy in adults due to the availability of other PIs with better safety profiles and less dosing frequency. The most common adverse drug reactions identified with cobicistat use are hyperbilirubinemia, jaundice, and rash.[10]

Table 5 outlines the most common adverse events and the Black Box warning information pertaining to combination products.

Table 5. Combination Products: Adverse Events and Black Box Warnings[9,10*]

Combination Product	Adverse Events		Black Box Warnings
	Incidence > 10%	**Incidence 1% to 10% or frequency not defined**	
Abacavir/Dolutegravir/ Lamivudine (ABC/DTG/3TC) Triumeq	• **Endo**: Hyperglycemia (≥126 mg/dL) • **GI**: ↑ serum lipase (>1.5 x ULN) • **NMS**: ↑ creatine phosphokinase (≥6.0 x ULN)	• **CNS**: Drowsiness (<2%), lethargy (<2%), nightmares (<2%), sleep disorder (<2%), suicidal ideation (<2%), depression, fatigue, headache, insomnia • **Derma**: Pruritus (<2%) • **Endo**: Hypertriglyceridemia (<2%) • **GI**: Abdominal distention (<2%), abdominal distress (<2%), abdominal pain (<2%), anorexia (<2%), dyspepsia (<2%), flatulence (<2%), gastroesophageal reflux disease (<2%), upper abdominal pain (<2%), vomiting (<2%) • **Hema&onco**: ↓ neutrophils • **Hepatic**: Hepatitis (<2%), ↑ serum ALT (>2.5 x ULN), ↑ serum AST (>2.5 x ULN) • **NMS**: Arthralgia (<2%), myositis (<2%) • **Renal**: Renal insufficiency (<2%) • **Misc**: Fever (<2%)	• Hypersensitivity Reactions (Patients who carry the HLA-B*5701 allele are at a higher risk) • Lactic Acidosis and Severe Hepatomegaly with Steatosis • Exacerbations of Hepatitis B
Abacavir sulfate/Lamivudine (ABC/3TC) Epzicom	• **CNS**: Abnormal dreams, anxiety, depression, dizziness, fatigue, headache, insomnia, malaise, migraine, vertigo • **Derma**: Skin rash • **GI**: Abdominal pain, diarrhea, gastritis • **HS**: HS (including multiorgan failure and anaphylaxis; ≤9%; higher incidence in subjects carrying the HLA-B*5701 allele) • **Misc**: Fever	• **GI**: Diarrhea (5%), Nausea (5%) • **Neur**: Dizziness, Headache (7%), Insomnia (7%), Vertigo • **Psy**: Depression (7%) • **CNS**: Fatigue, Malaise • **Immuno**: Hypersensitivity reaction (9%) <u>Serious AEs</u> (*frequencies not available*): • **CV**: Myocardial infarction • **Derm**: Stevens-Johnson syndrome, Toxic epidermal necrolysis • **Endo**: Lactic acidosis • **GI**: Pancreatitis • **Hema**: Anemia, Thrombocytopenia • **Hepatic**: Hepatomegaly (Severe), Hepatotoxicity, Reactivation of hepatitis B viral hepatitis, Steatosis of liver • **Immuno**: Immune reconstitution syndrome	• Serious and fatal hypersensitivity reactions reported with ABC (Patients who carry the HLA-B*5701 allele are at a higher risk) • Lactic acidosis and severe hepatomegaly with steatosis • Severe exacerbation of hepatitis B in patients coinfected with HIV-1 and HBV and in those who have discontinued lamivudine
Abacavir/Lamivudine/ Zidovudine (ABC/3TC/ZDV) Trizivir	• **GI**: Nausea (Moderate to Severe) (19%), Nausea and vomiting (Moderate to Severe) (10%) • **Neur**: Headache (Moderate to Severe) (13%) • **CNS**: Headache (13%), fatigue (12%), malaise (12%)	• **CNS**: depression (6%), anxiety (5%) • **Resp**: Viral respiratory infection (5%) • **Immuno**: Hypersensitivity reaction (1% to 8%) • **Derma**: Skin rash (5%) • **Endo**: ↑ amylase (2%), ↑ serum triglycerides (grade 3-4: 2%), ↑ gamma-glutamyl transferase, redistribution of body fat • **Hema&onco**: Neutropenia (5%) • **Hepatic**: ↑ serum ALT (6%)	• Serious and fatal hypersensitivity reactions reported with ABC (Patients who carry the HLA-B*5701 allele are at a higher risk) • Lactic acidosis and severe hepatomegaly with steatosis • Severe exacerbation of hepatitis B in patients coinfected with HIV-1 and HBV and in those who have discontinued lamivudine

Combination Product		Adverse Events	Black Box Warnings
		• **Infection**: Viral infection (5%) • **Misc**: Fever and chills (6%)	
Atazanavir/Cobicistat ATV/c Evotaz	• **Hepatic**: Abnormal bilirubin levels (65%; >2.5 × ULN), jaundice (13%; grades 2 to 4: 5%) • **Ophth**: Scleral icterus (15%; grades 2 to 4: 3%) • **GI**: Nausea (12%)	• **CV**: First-degree atrioventricular block (6%; asymptomatic), cardiac conduction disturbance (including but not limited to P-R interval prolongation and second degree atrioventricular block) • **CNS**: Abnormal dreams (grades ≥2: <2%), depression (grades ≥2: <2%), fatigue (grades ≥2: <2%), headache (grades ≥2: <2%), insomnia (grades ≥2: <2%) • **Derma**: Skin rash (5%; erythema multiforme, maculopapular rash, eosinophilia, and DRESS syndrome), Stevens-Johnson syndrome • **Endo**: Glycosuria (3%; ≥1,000 mg/dL), ↑ gamma-glutamyl transferase (2%; >5.0 × ULN), Fanconi's syndrome (grades ≥2: <2%), buffalo hump, cushingoid appearance, ↑ HDL cholesterol, ↑ LDL cholesterol, ↑ serum cholesterol, ↑ serum triglycerides, truncal obesity • **GI**: Nausea (12%; grades 3/4: 2%), diarrhea (11%; grades ≥2: <2%), ↑ serum lipase (grades 3/4: 9%), ↑ serum amylase (4%; >2.0 × ULN), upper abdominal pain (grades ≥2: <2%), vomiting (grades ≥2: <2%) • **GU**: Hematuria (3%; >75 RBC/HPF), breast hypertrophy • **Hema&onco**: Hemorrhage (increased spontaneous bleeding in patients with hemophilia) • **Hepatic**: ↑ serum ALT (3%; >5.0 × ULN), ↑ serum AST (3%; >5.0 × ULN), hepatotoxicity (in patients with hepatitis) • **Immuno**: Immune reconstitution syndrome • **NMS**: ↑ creatine phosphokinase (5%; ≥10.0 × ULN), rhabdomyolysis (<2%), amyotrophy, lipoatrophy • **Renal**: Nephrolithiasis (2%), renal disease (grades ≥2: <2%), acute renal failure, ↓ creatinine clearance, ↑ serum creatinine, renal insufficiency	
Darunavir/Cobicistat DRV/c Prezcobix	Not described	• **CNS**: Headache (3%) • **Derma**: Skin rash (5% to 16%) • **GI**: Diarrhea (5%), nausea (4%), vomiting (2%), abdominal pain (1%), flatulence (1%) • **Hepatic**: ↑ liver enzymes (1%) • **HSR**: Drug-induced hypersensitivity (2%) • **Immuno**: Immune reconstitution síndrome <u>Serious AEs</u> *(frequencies not available)* • **Derma**: Skin reaction extreme, Stevens-Johnson syndrome	Black box not available

Combination Product		Adverse Events	Black Box Warnings
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate EFV/FTC/TDF Atripla	• **Endo**: Hypercholesterolemia (22%) • **Psychiatric**: abnormal dreams (>10%)	• **CNS**: Depression (9%), fatigue (9%), dizziness (8%), headache (6%), anxiety (5%), insomnia (5%), drowsiness (4%), abnormal dreams • **Derma**: Skin rash (7%) • **Endo**: ↑ serum triglycerides (4%), hyperglycemia (2%) • **GI**: Diarrhea (9%), nausea (9%), ↑ serum amylase (8%), vomiting (2%) • **GU**: Hematuria (3%) • **Hema&onco**: Neutropenia (3%) • **Hepatic**: ↑ serum AST (3%), increased serum ALT (2%), ↑ serum alkaline phosphatase (1%) • **NMS**: ↑ creatine phosphokinase (9%) • **Resp**: Sinusitis (8%), upper respiratory tract infection (8%), nasopharyngitis (5%)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC or TDF (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Elvitegravir/Cobicistat/ Emtricitabine/ Tenofovir Alafenamide Fumarate EVG/c/FTC/TAF Genvoya	• **NMS**: Decreased bone mineral density (≥5% decrease at lumbar spine: 12%; ≥7% decrease at femoral neck: 11%)	• **CNS**: Headache (6%), fatigue (5%) • **Endo**: ↑ LDL cholesterol, ↑ serum cholesterol • **GI**: Nausea (10%), diarrhea (7%)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Elvitegravir/Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate EVG/c/FTC/TDF Stribild	• **GI**: Nausea (16%), diarrhea (12%) • **GU**: Proteinuria (52%) • **Renal**: Increased serum creatinine (7% to 12%)	• **CNS**: Abnormal dreams (9%), headache (7%), fatigue (4%), dizziness (3%), insomnia (3%), drowsiness (1%) • **Derma**: Skin rash (4%) • **Endo**: ↑ amylase (3%), ↑ serum cholesterol (grades 3/4: ≤1%), ↑ serum triglycerides (grades 3/4: ≤1%) • **GI**: Flatulence (2%) • **GU**: Hematuria (4%) • **Hepatic**: ↑ serum AST (3%), increased serum ALT (2%) • **NMS**: ↑ creatine phosphokinase (8%), bone fracture (4%)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC or TDF (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Emtricitabine/Rilpivirine/Tenofovir Alafenamide Fumarate FTC/RPV/TAF Odefsey	**Package insert**: **GI**: nausea (*due to Emtricitabine and Tenofovir Alafenamide)*	<u>Common</u> **GI**: Nausea **Neur**: Headache, Somnolence <u>Serious adverse events</u> • **Derma**: Disorder of skin (Severe) • **Endo**: Lactic acidosis • **Hepatic**: Hepatitis B, Exacerbation, Hepatomegaly, With steatosis, Hepatotoxicity	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)

Combination Product	Adverse Events		Black Box Warnings
		• **Immuno**: Drug reaction with eosinophilia and systemic symptoms, Hypersensitivity reaction, Immune reconstitution syndrome • **NMS**: Decreased bone mineral density, Fracture of bone • **Psychiatric**: Depression, Injury due to suicide attempt, Suicidal thoughts • **Renal**: Acute renal failure, Fanconi syndrome, Renal impairment	
Emtricitabine/Rilpivirine /Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) Complera	• **Endo**: ↑ serum cholesterol (≤14%), ↑ LDL cholesterol (1% to 13%) • **Hepatic**: ↑ serum ALT (1% to 19%), ↑ serum AST (1% to 16%)	• **CNS**: Depression (2% to 9%), headache (2%), insomnia (2%) • **Endo**: Adrenocortical insufficiency (7%; not associated with any serious events) • **Hepatic**: ↑ serum bilirubin (1% to 6%) • **Renal**: ↑ serum creatinine (≤6%)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC and/or TDF (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) Truvada	• **Derma**: Rash (10% or greater) • **Neuro**: Insomnia (10% or greater) • **Psychiatric**: Dream disorder (10% or greater)	• **GI**: Abdominal pain (HIV-1 infected patients, 5% or greater; HIV-1 uninfected subjects, 4%), Diarrhea (9%), Nausea (9%), Serum amylase raised (8%) • **NMS**: Backache (5% or greater), Myalgia (5% or greater), Osteopenia • **Neuro**: Dizziness (8%), Headache (HIV-1 infected patients, 6%; uninfected subjects, 7%), Peripheral neuropathy (5% or greater) • **Psychiatric**: Depression (9%), • **Resp**: Pneumonia (5% or greater) • **CNS**: Fatigue (9%)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HIV-1 and HBV who have discontinued Truvada (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Emtricitabine/Tenofovir Alafenamide Fumarate (FTC/TAF) Descovy	• **GI**: Nausea (10%) • **NMS**: Decreased bone mineral density (≥5% decrease at lumbar spine: 1% to 10%; ≥7% decrease at femoral neck: 1% to 7%), bone fracture (≤1%; excluding fingers and toes)	• **Endo**: Increased HDL cholesterol, increased LDL cholesterol, increased serum cholesterol, increased serum triglycerides • **Hepatic**: Exacerbation of hepatitis B • **Renal**: ↑ serum creatinine (mean increase 0.1 mg/dL)	• Lactic acidosis and severe hepatomegaly with steatosis • Severe, acute exacerbations of hepatitis B have occurred in patients coinfected with HBV and HIV-1 who have discontinued FTC and/or TDF (If patients are coinfected with HBV and HIV-1, monitor hepatic function closely)
Lamivudine/Zidovudine 3TC/AZT Combivir	• **GI**: Diarrhea (18%), Loss of appetite (10%), Nausea (33%), Nausea and vomiting (13%) • **NMS**: Musculoskeletal pain (12%)	• **Derma**: Rash (9%), Erythema multiforme, Stevens-Johnson syndrome • **GI**: Abdominal pain (9%), Pancreatitis • **NMS**: Myalgia (8%), Rhabdomyolysis • **Other**: Fatigue, Fever • **Hema**: Anemia (2.9%), Neutropenia (7.2%)	• Hematologic toxicity including neutropenia and severe anemia • Symptomatic myopathy associated with prolonged use of zidovudine • Lactic acidosis and severe hepatomegaly with steatosis

Combination Product	Adverse Events		Black Box Warnings
	• **Neuro**: Dizziness (10%), Headache (35%), Insomnia (11%), Neuropathy (12%), Sleep disorder (11%) • **Resp**: Cough (18%), Nasal symptoms OS (20%)	• **Hepatic**: Hepatomegaly (Severe), Steatosis of liver (Severe) • **Immuno**: Anaphylaxis, Hypersensitivity reaction	• Exacerbations of Hepatitis B in patients who are co-infected with hepatitis B virus HIV-1 and have discontinued lamivudine
Lopinavir/Ritonavir LPV/r Kaletra	• **Derma**: Skin rash (children 12%; adults ≤5%) • **Endo**: Hypercholesterolemia (3% to 39%), increased serum triglycerides (3% to 36%), increased gamma-glutamyl transferase (10% to 29%) • **GI**: Diarrhea (7% to 28%; greater with once-daily dosing), dysgeusia (children 22%; adults <2%), vomiting (children 21%; adults 2% to 7%), nausea (5% to 16%), abdominal pain (1% to 11%) • **Hepatic**: Increased serum ALT (grade 3/4: 1% to 11%) • **Resp**: Upper respiratory tract infection (14%)	>2% to 10%: • **CV**: Vasodilation (≤3%) • **CNS**: Fatigue (8%, including weakness), headache (2% to 6%), anxiety (4%), insomnia (≤4%) • **Derma**: Skin infection (3%, including cellulitis, folliculitis, furuncle) • **Endo**: Hypertriglyceridemia (6%), hyperglycemia (≤5%), hyperuricemia (≤5%), alteration in sodium (children 3%), weight loss (≤3%) • **GI**: ↑ serum amylase (3% to 8%), dyspepsia (≤6%), ↑ serum lipase (3% to 5%), flatulence (1% to 4%), gastroenteritis (3%) • **Hema&onco**: Thrombocytopenia (grade 3/4: 4% children), neutropenia (grade 3/4: 1% to 5%) • **Hepatic**: ↑ serum AST (grade 3/4: 2% to 10%), hepatitis (4%, including increased AST, ALT, and gamma-glutamyl transferase), ↑ serum bilirubin (children 3%; adults 1%) • **HSR**: Hypersensitivity (3%, including urticaria and angioedema) • **NMS**: Weakness (≤9%), musculoskeletal pain (6%) • **Resp**: Lower respiratory tract infection (8%)	Black box not available

* See individual agents as well as other combination products for additional information.

Key to Abbreviation: CNS=central nervous system; CV=cardiovascular; Derm=dermatologic: Endo=Endocrine; GI=gastrointestinal; GU=genitourinary; Hema&onco=hematologic and oncologic; HSR=hypersensitivity reaction; ICP=intracranial pressure; Immuno= Immunologic; Metab=metabolic; Misc=miscellaneous; Neur= Neurologic; NMS=neuromuscular system; Onc=oncologic; Ophth=Opthamologic; Other=rare or case reports; Psy= Psychiatric; Resp=respiratory

Summary

Fixed-dose combination products formulated in a single pill have become the current hallmark of antiretroviral treatment in HIV-infected patients. The most appropriate and tolerable combination product should be prescribed in order to maximize adherence to ART regimens, reduce the morbidity and mortality associated to HIV-infection and prevent HIV transmission.

The goal of HIV therapy is to combine at least three antiretroviral (ARV) agents into a regimen that effectively suppresses viral replication to undetectable levels, delays disease progression, and prevents the development of resistance (also known as highly active antiretroviral therapy or HAART). According to international and national current guidelines, the standard of care for the initial treatment of HIV-infected patients (i.e treatment naïve patients) generally involves two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third ARV agent: a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor (INSTI) or a protease inhibitor (PI) boosted with a pharmacokinetic enhancer.

Four meta-analyses and nine RCTs reporting direct head-to-head efficacy comparisons were identified for evaluation. Among the fourteen antiretroviral fixed dose combinations (FDC) available in the U.S., eight were studied in at least one comparative clinical trial. No head-to-head comparisons for initial HIV treatment were identified for the most newly approved combination products FTC/RPV/TAF (Odefsey) and FTC/TAF (Descovy), which were approved by the FDA in April 2016 and March 2016, respectively. Evidence is also lacking for ATV/c (Evotaz), DRV/c (Prezcobix), ABC/3TC/ZDV (Trizivir) and LPV/r (Kaletra). Some trials have suggested less efficacy for Trizivir compared to NNRT-based regimens, and therefore it is not recommended by the U.S. guidelines. LPV/r together with 2 NRTIs is no longer recommended for initial therapy in adults due to the availability of other PIs with better safety profiles and less dosing frequency. These may be potential reasons explaining the lack of head-to-head comparisons.

Based on the evidence identified, six relevant fixed-dose combination comparisons met the criteria for inclusion. Among them, three triple fixed-dose combinations were compared to the standard of care (EFV/FTC/TDF) at the time of the study. From an efficacy point of view, most systematic reviews and comparative randomized controlled trials showed no significant differences between FDCs. Few studies demonstrated superior efficacy of one FDC versus another FDC. The available evidence supports the current U.S. treatment guideline recommendations with respect to the recommended and alternative regimen options established for HIV treatment naïve patients. DTG/ABC/3TC was superior to EFV/FTC/TDF in the studies identified, and it is recommended by the U.S. guidelines as the preferred drug regimen if the HLA-B*5701 (a specific human genetic variation) screening test is negative. RPV/FTC/TDF was noninferior to EFV/FTC/TDF in the overall population at week 96 with respect to virological suppression, while some subgroups of patients (i.e. patients with baseline HIV RNA≤100,000

copies/mL and CD4 >200 cells/µl) receiving RPV/FTC/TDF demostarted superior efficacy compared to EFV/FTC/TDF. RPV/FTC/TDF is classified as an alternative regimen option by U.S. guidelines for patients with HIV RNA <100,000 copies/mL and CD4 >200 cells/µl. Furthermore, several studies demonstrated noninferior efficacy of the backbone of TDF/FTC versus ABC/3TC, whereas one study indicated a more rapid time to virologic failure for ABC/3TC plus ATV/r or EFV compared to TDF/FTC plus ATV/r or EFV in patients with HIV RNA<100,000 copies/mL. Current guidelines consider TDF/FTC as recommended backbone when combined with dolutegravir, elvitegravir/cobicistat, raltegravir or darunavir/ritonavir. ABC/3TC is also considered a recommended backbone in combination with dolutegravir if HLA-B*5701 test is negative. In addition, ABC/3TC is considered as "other regimen option" backbone for patients with HIV RNA<100,000 copies/mL and HLA-B*5701 negative when combined with efavirenz, atazanavir/ritonavir, atazanavir/cobicistat and raltegravir. Use of a ZDV/3TC backbone resulted in similar or reduced efficacy and a worse safety profile compared to TDF/FTC. Current guidelines do not recommend the use of a ZDV/3TC backbone for non-pregnant adults. However, it is considered an alternative regimen for pregnant women. If tenofovir is included as part of an antiretroviral (ARV) combination, it should be considered that TAF-containing combinations have demonstrated similar efficacy, better renal and bone safety profiles, and higher incidence of lipid abnormalities compared to TDF-containing combinations. TAF/FTC, RPV/FTC/TAF, ATV/c and DRV/c are recommended by current guidelines, based on switching or bioequivalence studies, but no direct head-to-head comparisons with a single tablet formulation have been identified. Evidence is also lacking for ABC/3TC/ZDV and LPV/r. ABC/3TC/ZDV is not recommended by the U.S. guidelines and LPV/r is only recommended in some specific groups of patients such as children and pregnant women. Ultimately, treatment decisions should be based on individual patient characteristics and the safety profile of the various ARV medications.

Most of the trials identified included adult patients. Limited efficacy and safety data in pediatric and geriatric population was found. Recommendations for pregnant women are stated in the US guidelines.

The safety profile of fixed dose combinations is characterized by the combination of the adverse events of each component. Considering the studies identified, combinations containing abacavir are known to cause hypersensitivity reactions and increases in lipid parameters. Combinations containing tenofovir disoproxil fumarate are typified by renal and bone toxicity; and tenofovir alafenamide may alter some lipid parameters. Efavirenz combinations are defined by neuropsychiatric, rash and lipid events. Rilpivirine combinations may cause adverse events similar to efavirez combinations, but less commonly. The backbone containing zidovudine and lamivudine is characterized by hematologic disorders such as anemia and neutropenia, resulting in decreased use for HIV treatment. Finally, integrase inhibitor co-formulations including dolutegravir or elvitegravir have been shown to be well-tolerated, with a lower incidence of central nervous system events than efavirenz combinations. Didanosine and stavudine are NRTI

agents associated with a high risk of mitochondrial toxicity, which has caused the exclusion of these agents from the fixed dose combination market and generally, from the current HIV recommended treatment options.

Adherence to antiretroviral drugs is crucial to accomplish HIV treatment success. Before initiation of ART, patients should receive education outlining the importance of adherence in order to avoid drug-resistance, maintain the maximal virological suppression, and ultimately, improve quality of life. Numerous studies have demonstrated an increase of adherence rate in those patients receiving treatment with single-tablet regimens compared to those on multiple-tablet regimens.

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Appendix A. FDA-Approved Antiretroviral Agents for the Treatment of HIV-1[9-11]*

Nucleoside & Nucleotide Reverse Transcriptase Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Integrase Strand Transfer Inhibitors	Protease Inhibitors	Entry Inhibitors	Pharmacokinetic Enhancer
Abacavir (ABC) • Ziagen: ABC • Epzicom: ABC/3TC • Trizivir: ABC/ZDV/3TC • Triumeq: ABC/3TC/DTG	**Delavirdine (DLV)** • Rescriptor: DLV	**Dolutegravir (DTG)** • Tivicay: DTG • Triumeq: ABC/3TC/DTG	**Atazanavir (ATV)** • Reyataz: ATV • Evotaz: ATV/c	**Enfuvirtide (ENF)** • Fuzeon: ENF	**Cobicistat (c or COBI)** •Tybost: c •Evotaz: ATV/c • Genvoya: FTC/EVG/c /TAF • Prezcobix: DRV/c • Stribild: EVG/c /TDF/FTC
Didanosine (ddI) • Videx: ddI	**Efavirenz (EFV)** • Sustiva: EFV • Atripla: EFV/TDF/FTC	**Elvitegravir (EVG)** • Genvoya: FTC/EVG/c /TAF • Stribild: FTC/EVG/c /TDF	**Darunavir (DRV)** • Prezista: DRV • Prezcobix: DRV/c	**Maraviroc (MVC)** • Selzentry: MVC	**Ritonavir (r or RTV)** • Norvir: r • Kaletra: r/LPV
Emtricitabine (FTC) • Emtriva: FTC • Atripla: EFV/TDF/ FTC • Complera: RPV/TDF/FTC • Descovy: FTC/TAF • Genvoya: FTC/EVG/COBI/TAF • Odefsey: RPV/TAF/FTC • Stribild: FTC/EVG/COBI/TDF • Truvada: FTC/TDF	**Etravirine (ETR)** • Intelence: ETR	**Raltegravir (RAL)** • Isentress: RAL	**Fosamprenavir (FPV)** • Telzir: FPV		
Lamivudine (3TC) • Epivir: 3TC • Combivir: 3TC/ZDV • Epzicom: 3TC/ABC • Trizivir: 3TC/ZDV/ABC • Triumeq: 3TC/ABC/DTG	**Nevirapine (NVP)** • Viramune: NVP		**Indinavir (IDV)** • Crixivan: IDV		
Stavudine (d4T) • Zerit: d4T	**Rilpivirine (RPV)** • Edurant: RPV • Complera: RPV/ TDF/FTC • Odefsey: RPV/ TAF/ FTC		**Lopinavir (LPV)** • Kaletra: r/LPV		
Tenofovir alafenamide (TAF) • Vemlidy: TAF • Descovy: FTC/TAF • Genvoya: FTC/EVG/COBI/TAF • Odefsey: RPV/TAF/FTC			**Nelfinavir (NFV)** • Viracept: NFV		

Nucleoside & Nucleotide Reverse Transcriptase Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Integrase Strand Transfer Inhibitors	Protease Inhibitors	Entry Inhibitors	Pharmacokinetic Enhancer
Tenofovir disoproxil (TDF) • Viread: TDF • Atripla: EFV/TDF/ FTC • Complera: RPV/TDF/FTC • Stribild: FTC/EVG/COBI/TDF • Truvada: FTC/TDF			**Ritonavir (r or RTV)** • Norvir: r • Kaletra: r/LPV		
Zidovudine (ZDV or AZT) • Retrovir: ZDV • Combivir: ZDV/3TC • Trizivir: ZDV/3TC/ABC			**Saquinavir (SQV)** • Invirase: SQV **Tipranavir (TPV)** • Aptivus: TPV		

* Drug agents are grouped by generic name and abbreviation in bold; brand-names and constituents are listed in bullets.

Abbreviation key: 3TC-lamivudine, ABC-abacavir, ATV-atazanavir, AZT-zidovudine, c-cobicistat, COBI-cobicistat d4T-stavudine, ddl-didanosine, DVL-delavirdine, DRV-darunavir, DTG-dolutegravir, EFV-efavirenz, ETR-etravirine, EVG-elvitegravir, FTC-emtricitabine, IDV- indinavir, LPV- lopinavir, MVC-maraviroc, NFV- nelfinavir, NVP- Nevirapine, RAL-raltegravir, RPV- rilpivirine, RTV-ritonavir, SAQ-saquinavir, TAF-tenofovir alafenamide, TDF tenofovir disoproxil, TPV-tipranavir, ZDV-zidovudine

Appendix B. MEDLINE & EMBASE Literature Search Strategies for Nucleoside/Nucleotide Reverse Transcriptase Inhibitors and Combination Products

Ovid MEDLINE
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to February 24, 2017>
Systematic Review and Randomized Controlled Trials Search Strategy (January 26, 2017)
1 Emtricitabine/ (866)
2 (Emtricitabin$ or Emtriva$ or coviracil$).ti,ab,kw,kf,rn. (2128)
3 Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ (229)
4 (atripla$ orcombivir$ or complera$ or descovy$ or genvoya$ or kaletra$ or odefsey$ or stribild$ or truvada$).ti,ab,kw,kf,rn. (346)
5 (tenofovir alafenamid$ or tenofovir disoproxi$ or vemlidy or viread).ti,ab,kw,kf,rn. (1370)
6 (abacavir sulfate? or triumeq$ or epzicom$ or ziagen).ti,ab,kw,kf,rn. (116)
7 ((atazanavir or darunavir$) adj2 cobicistat$).ti,ab,kw,kf,rn. (42)
8 (kivexa$ or evotaz$ or prezcobix$).ti,ab,kw,kf,rn. (17)
9 Didanosine/ (1949)
10 (DIDANOSIN$ or videx? or dideoxyinosin$ or ((ddi or ddl) adj2 (anti-viral? or antiviral?))).ti,ab,kw,kf,rn. (2993)
11 Lamivudine/ (6010)
12 (Lamivudin$ or Epivir$).ti,ab,kw,kf,rn. (9356)
13 Stavudine/ (1752)
14 (Stavudin$ or Zerit$).ti,ab,kw,kf,rn. (2936)
15 Zidovudine/ (9356)
16 (Zidovudin$ or Retrovir$ or azidothymidin$ or (AZT adj2 (antiviral? or anti-viral?))).ti,ab,kw,kf,rn. (54091)
17 Lopinavir/ or RItonavir/ (4110)
18 (lopinavir$ or ritonavir$).ti,ab,kw,kf,rn. (6614)
19 or/1-18 [Drugs of Interest NRTI] (69760)
20 (RNA directed RNA polymerase$ or DNA dependent RNA polymerase$).ti,kw,kf. (739)
21 *rna-directed dna polymerase/ or *hiv reverse transcriptase/ (5335)
22 (RNA directed RNA polymerase$ or DNA dependent RNA polymerase$).ab. (1178)
23 or/20-22 [NRTI-MeSH] (6981)
24 exp HIV/ (89680)
25 (HIV or (AIDS adj2 (lentivirus$ or retrovirus$ or viral$ or virus$))).ti,ab,kw,kf. (273096)
26 (Lymphadenopath$ adj2 (retrovirus$ or virus$)).ti,ab,kw,kf. (345)
27 ((human or acquired) adj2 (immunodefc$ or immuno deficienc$ or immune deficienc$) adj virus$).ti,ab,kw,kf. (556)
28 ((human immuno or immunodeficienc$) adj2 virus$).ti,ab,kw,kf. (83915)
29 ("Human T Cell Lymphotropic Virus$" or " Human T Cell Leukemi$ Virus$").ti,ab,kw,kf. (5102)
30 (LAV-HTLV or LAVHTLV or (LAV adj AIDS)).ti,ab,kw,kf. (222)
31 or/24-30 [HIV/AIDS] (304070)
32 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (1102420)
33 exp animals/ not humans.sh. (4323937)
34 32 not 33 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] (1017366)

35 (metaanaly$ or meta-analy$).ti,kw,kf,pt,ab. (126618)
36 (systematic adj2 review).ti,kw,kf. (68798)
37 (or/35-36) not 33 [SR-Filter- not validated] (162816)
38 and/19,31,34 [RCT -DRUGS & HIV] (3973)
39 (and/23,31,34) not 38 [RCT RNA-Directed & HIV] (39)
40 (and/19,31,37) not (or/38-39) [SR Results --DRUGS & HIV] (104)
41 (and/23,31,37) not (or/33,38-40) [SR-Results-RNA-Directed & HIV] (1)
42 38 or 39 (4012)
43 40 or 41 (105)
44 remove duplicates from 42 [RCT Results HIV 3] (3736)
45 remove duplicates from 43 [SR Results HIV 3] (102)

EMBASE (via EMBASE.com)

Systematic Review Search Strategy (February 24, 2017)

SEARCH QUERY

((((('didanosine'/mj or 'emtricitabine'/mj or 'lamivudine'/mj or 'stavudine'/mj or 'zidovudine'/mj) or (didanosin*:ti,ab or videx*:ti,ab or dideoxyinosin*:ti,ab) or (ddi near/2 (antiviral* or 'anti viral*')):ti,ab or ('nsc 612049':ti,ab or nsc612049:rn,ti,ab) or ('emtricitabine plus rilpivirine plus tenofovir disoproxil'/de or 'emtricitabine plus rilpivirine plus tenofovir alafenamide'/de) or (emtricitabin*:ti,ab or emtriva*:ti,ab or coviracil*:ti,ab) or (lamivudin*:ti,ab or epivir*:ti,ab) or (stavudin*:ti,ab or zerit*:ti,ab) or (zidovudin*:ti,ab or retrovir*:ti,ab or azidothymidin*:ti,ab) or (atz near/2 (antiviral* or 'anti viral*')):ti,ab or 'rna directed dna polymerase inhibitor'/mj or ('delavirdine'/de or 'efavirenz plus emtricitabine plus tenofovir disoproxil'/de or 'rilpivirine'/de) or 'nonnucleoside reverse transcriptase inhibitor'/mj or 'reverse transcriptase inhibitor*':ti,ab or ((hiv near/2 'reverse transcriptas*'):ti,ab or (('non nucleosid*' or nonnucleosid* or nonnucleotid* or 'non nucleotid*') near/2 reverse):ti,ab and transcriptas*:ti,ab) or 'efavirenz'/mj or (efavirenz*:ti,ab or sustiva*:ti,ab or etravirine*:ti,ab) or 'rna directed dna polymerase'/mj or (nnrti:ti,ab or nnrtis:ti,ab) or (delarvidin*:ti,ab or delavirdin*:ti,ab or delaviridin*:ti,ab) or (efavirenz:ti,ab or efavir:ti,ab or filginase*:ti,ab or stocrin*:ti,ab or sustiva*:ti,ab or virorrever*:ti,ab) or (l743726:ti,ab or 'l 743726':ti,ab or 'l-743,726':ti,ab or 'l-743726':ti,ab or 'l 743,726':ti,ab or 'dmp 266':ti,ab or dmp266:ti,ab or 'dmp-266':ti,ab or je6h2o27p8:ti,ab,rn) or (etravirine:ti,ab or intelence:ti,ab) or ('r 165335;':ti,ab or 'r165335':ti,ab or 'tmc 125':ti,ab or 'tmc125':ti,ab or '269055-15-4':ti,ab or '269055154':ti,ab,rn) or (rilpivirine:ti,ab,rn or r278474:ti,ab,rn or tmc278:ti,ab,rn or 'tmc 278':ti,ab,rn or fi96a8x663:ti,ab,rn)) and ('human immunodeficiency virus'/exp/mj or (hiv:ti,ab or (aids near/3 hiv):ti,ab or 'acquired immuno* deficiency':ti,ab or 'acquired immunodeficienc*':ti,ab))) and ((metaanaly*:ti,ab or 'meta analy*':ti,ab or (systematic near/2 review):ti) or ('systematic review'/mj or 'meta analysis'/mj)) not ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de not ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de and ('human'/exp or 'human cell'/de))) and [english]/lim) not 'conference abstract'/it

Randomized Controlled Trials Search Strategy (February 24, 2017)

SEARCH QUERY

((((('didanosine'/mj or 'emtricitabine'/mj or 'lamivudine'/mj or 'stavudine'/mj or 'zidovudine'/mj) or (didanosin*:ti,ab or videx*:ti,ab or dideoxyinosin*:ti,ab) or (ddi near/2 (antiviral* or 'anti viral*')):ti,ab or ('nsc 612049':ti,ab or nsc612049:rn,ti,ab) or ('emtricitabine plus rilpivirine plus tenofovir disoproxil'/de or 'emtricitabine plus rilpivirine plus tenofovir alafenamide'/de) or (emtricitabin*:ti,ab or emtriva*:ti,ab or coviracil*:ti,ab) or (lamivudin*:ti,ab or epivir*:ti,ab) or (stavudin*:ti,ab or zerit*:ti,ab) or (zidovudin*:ti,ab or retrovir*:ti,ab or azidothymidin*:ti,ab) or (atz near/2 (antiviral* or 'anti viral*')):ti,ab or 'rna directed dna polymerase inhibitor'/mj or ('delavirdine'/de or 'efavirenz plus emtricitabine plus tenofovir disoproxil'/de or 'rilpivirine'/de) or 'nonnucleoside reverse transcriptase inhibitor'/mj or 'reverse transcriptase inhibitor*':ti,ab or ((hiv near/2 'reverse transcriptas*'):ti,ab or (('non nucleosid*' or nonnucleosid* or nonnucleotid* or 'non nucleotid*') near/2 reverse):ti,ab and transcriptas*:ti,ab) or 'efavirenz'/mj or (efavirenz*:ti,ab or sustiva*:ti,ab or etravirine*:ti,ab) or 'rna directed dna polymerase'/mj or (nnrti:ti,ab or nnrtis:ti,ab) or (delarvidin*:ti,ab or

delavirdin*:ti,ab or delaviridin*:ti,ab) or (efavirenz:ti,ab or efavir:ti,ab or filginase*:ti,ab or stocrin*:ti,ab or sustiva*:ti,ab or virorrever*:ti,ab) or (l743726:ti,ab or 'l 743726':ti,ab or 'l-743,726':ti,ab or 'l-743726':ti,ab or 'l 743,726':ti,ab or 'dmp 266':ti,ab or dmp266:ti,ab or 'dmp-266':ti,ab or je6h2o27p8:ti,ab,rn) or (etravirine:ti,ab or intelence:ti,ab) or ('r 165335;':ti,ab or 'r165335':ti,ab or 'tmc 125':ti,ab or 'tmc125':ti,ab or '269055-15-4':ti,ab or '269055154':ti,ab,rn) or (rilpivirine:ti,ab,rn or r278474:ti,ab,rn or tmc278:ti,ab,rn or 'tmc 278':ti,ab,rn or fi96a8x663:ti,ab,rn)) and ('human immunodeficiency virus'/exp/mj or (hiv:ti,ab or (aids near/3 hiv):ti,ab or 'acquired immuno* deficiency':ti,ab or 'acquired immunodeficienc*':ti,ab))) and ('clinical study'/mj or 'clinical trial'/mj or 'controlled clinical trial'/mj or 'controlled study'/mj or 'major clinical study'/mj or 'randomized controlled trial'/mj or 'control group'/mj or ((clinical or randomi* or controlled or multicentre or multicenter or 'multi centre' or 'multi center') near/3 (study or trial)):ti,ab or placebo:ab,ti) not (((((('didanosine'/mj or 'emtricitabine'/mj or 'lamivudine'/mj or 'stavudine'/mj or 'zidovudine'/mj) or (didanosin*:ti,ab or videx*:ti,ab or dideoxyinosin*:ti,ab) or (ddi near/2 (antiviral* or 'anti viral*')):ti,ab or ('nsc 612049':ti,ab or nsc612049:rn,ti,ab) or ('emtricitabine plus rilpivirine plus tenofovir disoproxil'/de or 'emtricitabine plus rilpivirine plus tenofovir alafenamide'/de) or (emtricitabin*:ti,ab or emtriva*:ti,ab or coviracil*:ti,ab) or (lamivudin*:ti,ab or epivir*:ti,ab) or (stavudin*:ti,ab or zerit*:ti,ab) or (zidovudin*:ti,ab or retrovir*:ti,ab or azidothymidin*:ti,ab) or (atz near/2 (antiviral* or 'anti viral*')):ti,ab or 'rna directed dna polymerase inhibitor'/mj or ('delavirdine'/de or 'efavirenz plus emtricitabine plus tenofovir disoproxil'/de or 'rilpivirine'/de) or 'nonnucleoside reverse transcriptase inhibitor'/mj or 'reverse transcriptase inhibitor*':ti,ab or ((hiv near/2 'reverse transcriptas*'):ti,ab or (('non nucleosid*' or nonnucleosid* or nonnucleotid* or 'non nucleotid*') near/2 reverse):ti,ab and transcriptas*:ti,ab) or 'efavirenz'/mj or (efavirenz*:ti,ab or sustiva*:ti,ab or etravirine*:ti,ab) or 'rna directed dna polymerase'/mj or (nnrti:ti,ab or nnrtis:ti,ab) or (delarvidin*:ti,ab or delavirdin*:ti,ab or delaviridin*:ti,ab) or (efavirenz:ti,ab or efavir:ti,ab or filginase*:ti,ab or stocrin*:ti,ab or sustiva*:ti,ab or virorrever*:ti,ab) or (l743726:ti,ab or 'l 743726':ti,ab or 'l-743,726':ti,ab or 'l-743726':ti,ab or 'l 743,726':ti,ab or 'dmp 266':ti,ab or dmp266:ti,ab or 'dmp-266':ti,ab or je6h2o27p8:ti,ab,rn) or (etravirine:ti,ab or intelence:ti,ab) or ('r 165335;':ti,ab or 'r165335':ti,ab or 'tmc 125':ti,ab or 'tmc125':ti,ab or '269055-15-4':ti,ab or '269055154':ti,ab,rn) or (rilpivirine:ti,ab,rn or r278474:ti,ab,rn or tmc278:ti,ab,rn or 'tmc 278':ti,ab,rn or fi96a8x663:ti,ab,rn)) and ('human immunodeficiency virus'/exp/mj or (hiv:ti,ab or (aids near/3 hiv):ti,ab or 'acquired immuno* deficiency':ti,ab or 'acquired immunodeficienc*':ti,ab))) and ((metaanaly*:ti,ab or 'meta analy*':ti,ab or (systematic near/2 review):ti) or ('systematic review'/mj or 'meta analysis'/mj)) not ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de not ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de and ('human'/exp or 'human cell'/de))) and [english]/lim) or ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de not ('animal'/exp or 'invertebrate'/exp or 'animal experiment'/exp or 'animal model'/exp or 'animal tissue'/exp or 'animal cell'/exp or 'nonhuman'/de and ('human'/exp or 'human cell'/de)))) and [english]/lim) not 'conference abstract'/it

Appendix C. Summary of evidence for the Combination Products*

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
TAF/EVG/C/FTC (Genvoya) vs **TDF**/EVG/C/FTC (Stribild)					
Wang et al., 2016[45] **Meta-analysis** of 6 RCTs (Data extracted ONLY from the 4 RCTs in naïve patients: **Sax 2015**, Mills 2015, Sax 2014, **Wohl 2016***)*	HIV-1 infected treatment naïve adult patients TAF: 1947 patients TDF 1842 patients	**TAF/**ETG/C/FTC (TAF arm) vs **TDF**/ETG/C/FTC (TDF arm)	Naïve patients subgroup: <u>Primary endpoints at week 48</u>: • **Virologic suppression (HIV RNA < 50 c/mL)** TAF 90.2% vs TDF 89.5%; RR,1.01; 95%CI:0.99, 1.04 • **Virologic failure with resistance** TAF 0.72% vs TDF 0.65%; RR, 1.08; 95%CI: 0.52, 2.24 (No difference in efficacy between both treatment arms)	Naïve patients subgroup: <u>Safety endpoints at week 48</u>: **Safety and tolerability:** • AE rate**:** RR 0.99; 95%CI: 0.94, 1.05 • Laboratory abnormalities: RR 1.03; 95%CI: 0.86, 1.23 (TAF has similar tolerability and safety compared to TDF) **Bone outcomes** (mean percent BMD change from baseline) • *BMD spine*: TAF - 1.29% vs TDF –3.28% (p=0.002) • *BMD hip:* TAF –0.7% vs TDF –3.25% (p=0.005) **Renal outcome**s: • Mean decrease in eGFR-$_{CG}$ from BL: TAF -4.93 mL/min vs TDF -10.63 mL/min (p=0.007) • Mean increase in serum Cr from Baseline: TAF 0.065mg/dL vs TDF 0.095mg/dL (p=0.051) • RBP/Cr ratio (%): TAF 5.97 vs TDF 41.90 (p= 0.031) • b2-M/Cr ratio (%): TAF -35.87 vs TDF 8.90 (p=0.005) **Lipid outcomes:** • Mean change in total cholesterol: 33 TAF vs 12 mg/dL TDF, p=0.014 • Mean change HDL: 20 TAF vs 4.5 mg/dL TDF, p=0.008 • No differences in LDL cholesterol, triglycerides and total cholesterol/HDL	Include 2 phase 2 RCTs (Mills 2015 and Sax 2014)

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
				Discontinuations due to renal AE: TAF: 0 vs TDF: 10 patients (Renal and bone outcomes favored TAF vs. TDF)	
Wohl et al., 2016[47] [GS-US-292-0104 and GS-US-292-0111] 2 **RCTs** (Double-blind, phase 3, non-inferiority trials, **week 96** results) **Setting**: Study 104: 134 sites in North America, Europe, Australia, Japan, and Thailand Study 111: 128 sites in North America, Europe, and Latin America	1733 treatment naïve HIV-infected patients with CrCl ≥ 50 mL/min TAF group: 866 patients TDF group: 867 patients	**TAF/**ETG/C/FTC (TAF arm) vs **TDF**/ETG/C/FTC (TDF arm)	Primary endpoint at week 96: **% patients with HIV-1 RNA < 50 copies/mL at week 48** (NI margin: 12%) • Pooled studies: 86.6% vs 85.2%, 95%CI -1.8%, 4.8% (TAF vs TDF arm) Secondary endpoints at week 96: Virological failure with resistance (% patients): • Pooled studies: 1.2% vs 0.9% (TAF vs TDF arm) (Non-inferiority was demonstrated)	Overall safety: • Most common drug-related AEs (<10%): nausea, diarrhea and headache • Drug-related SAE: 5 vs 2 patients (TAF vs TDF arm) • Discontinuations due to AE: 1.2% vs 2.3% (TAF vs TDF arm) **Bone outcomes at week 96:** • % change from BL in spine BMD: –0.960% vs –2.792; p<0·001 (TAF vs TDF arm) • % change from BL in hip BMD: –0.672 vs –3.275, p<0·001 (TAF vs TDF arm) • Discontinuations due to > 5% decrease in BMD: 0 vs 3 patients (TAF vs TDF arm) **Renal outcomes at week 96:** • median change from baseline in estimated CrCl: 22.0 mL/min vs 27.5 mL/min, p≤0.001 (TAF vs TDF arm) • ↑ markers of proteinuria (UPCR, UACR, RBP/Cr and β2M/Cr) from BL in TDF arm vs TAF arm • Discontinuations due to renal AE: 0 vs 6 patients (TAF vs TDF arm) • **Lipid outcomes at week 96**: • ↑ from BL in total, LDL and HDL cholesterol, and triglycerides in TAF vs TDF arm (p<0.001) (Renal and bone outcomes favored TAF vs. TDF. Lipid outcomes favored TDF)	

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
Sax et al., 2015[46] [GS-US-292-0104 and GS-US-292-0111] 2 **RCTs** (Double-blind, phase 3, non-inferiority trials, **week 48** results) **Setting**: Study 104: 134 sites in North America, Europe, Australia, Japan, and Thailand Study 111: 128 sites in North America, Europe, and Latin America	1733 treatment naïve HIV-infected patients with CrCl ≥ 50 mL/min TAF group: 866 patients TDF group: 867 patients	**TAF**/ETG/C/FTC (TAF arm) vs **TDF**/ETG/C/FTC (TDF arm)	Primary endpoint at week 48: **% patients with HIV-1 RNA < 50 copies/mL at week 48** (NI margin: 12%) * Study 104: 93% vs 92%, 95% CI –2·6 to 4·5% (TAF vs TDF arm) * Study 111: 92% vs 89%, 95% CI –1·0 to 7·1% (TAF vs TDF arm) * Pooled studies: 92% vs 90%, adjusted difference 2.0%, 95% CI –0·7 to 4·7% (TAF vs TDF arm) Secondary endpoints at week 48: Pooled studies: **Virological failure** with resistance (% patients) 0.8% vs 0.6% (TAF vs TDF arm) Subgroup analysis: results on virological success * BL viral load <100000 copies/mL at BL: 94% vs 91% patients (TAF vs TDF arm) * Women: 95% vs 87% patients (TAF vs TDF arm) (Non-inferiority was demonstrated)	Overall safety: * Discontinuations due to AE: 0.9% vs 1.5% (TAF vs TDF arm) * Discontinuations due to AE related to study drugs: 0.8% vs 1.3% (TAF vs TDF arm) Bone outcomes at week 48: * BMD: < reduction in bone mineral density in TAF arm vs TDF arm - % change from BL in spine BMD: –1.30% vs –2.86; p<0·0001 (TAF vs TDF arm) - % change from BL in hip BMD: –0.66 vs –2.95, p<0·0001 (TAF vs TDF arm) - % patients with >3% spine bone loss: 26.5% vs 45.8% (TAF vs TDF arm) - % patients with >3% hip bone loss: 16.8% vs 50.1% (TAF vs TDF arm) Renal outcomes at week 48: * smaller ↓ in $eGFR\text{-}_{CG}$ in Group in TAF vs TDF * ↑ markers of proteinuria (UPCR, UACR, RBP/Cr and β2M/Cr) from BL in TDF arm vs TAF arm * Discontinuations due to renal AE: 0 vs 4 patients, p=0.03 (TAF vs TDF arm) Lipid outcomes at week 48: * > ↑ in total , LDL and HDL cholesterol and triglycerides in TAF vs TDF arm * Similar change in total cholesterol to HDL ratio in TAF vs TDF arm * % patients that started lipid-lowering drugs: 3.6% vs 2.9% (TAF vs TDF arm) (Renal and bone outcomes favored TAF vs. TDF. Lipid outcomes favored TDF)	* ↓ power to assess rare AEs (renal failure and fractures) * ↓% of women * ↓% of patients with advances HIV disease * Exclusion of patients with HBV * Absence of long-term data

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
EVG/c/FTC/TDF (Stribild) vs **EFV/FTC/TDF** (Atripla)					
Wohl et al., 2014[51] *[Study GS-US-236-0102]* **RCT** phase 3, double-blind, parallel assignment, non-inferiority trial (**week 144** results)	700 treatment naïve, ≥18 years, HIV RNA ≥ 5000 c/mL, any CD4 cell count, eGFR> 70 mL/min 348 with EVG/c/FTC/TDF 352 with EFV/FTC/TDF	EVG/c/FTC/TDF vs EFV/FTC/TDF with matching placebos	Primary endpoint at week 48: (EVG/c/FTC/TDF vs EFV/FTC/TDF) **% HIV RNA <50 c/mL** (by ITT, snapshot analysis, NI margin= 12%, 95% power): 80.2% vs 75.3% (difference 4.9%, 95%CI –1.3% to 11.1%) (Durable efficacy of EVG/c/FTC/TDF, with no new renal safety signal and a longer-term safety profile that is differentiated from EFV/FTC/TDF and is consistent with week 48 and 96)	Between W96 and W144: • No new or unexpected AE • Similar safety profile • Similar drug discontinuations due to AEs (6 EVG/c/FTC/TDF vs 7.4% EFV/FTC/TDF) • One patient discontinued due to an increase in Cr in EVG/c/FTC/TDF • More patients discontinued due to neuropsychiatric AEs and rash in EFV arm • No PRN cases	• ↓number of women • No patients with eGFR< 70 mL/min
Zolopa et al., 2013[50] *[Study GS-US-236-0102]* **RCT** phase 3, double-blind, parallel assignment, non-inferiority trial (**week 96** results)	700 treatment naïve, ≥18 years, HIV RNA ≥ 5000 c/mL, any CD4 cell count, eGFR> 70 mL/min 348 with EVG/c/FTC/TDF 352 with EFV/FTC/TDF	EVG/c/FTC/TDF vs EFV/FTC/TDF (standard-of-care) with matching placebos	Primary endpoint at week 48: (EVG/c/FTC/TDF vs EFV/FTC/TDF) **% HIV RNA <50 c/mL** (by ITT, snapshot analysis, NI margin= 12%, 95% power): 84% vs 82% (difference +2.7%, 95%CI –2.9% to 8.3%) (High rates of virologic suppression are maintained through week 96. Non-inferiority shown of EVG/c/FTC/TDF vs EFV/FTC/TDF). Long-term safety profile differentiated from EFV/FTC/TDF and consistent with week 48)	Between W48 and W96: • No new or unexpected AE • Similar safety profile • Similar drug discontinuations due to AEs (2 discontinued due to renal AEs in EVG/c/FTC/TDF) • Confirmation of Cr increases (>0.4 mg/dL) in EVG/c/FTC/TDF due to cobicistat. Recommendation included in the package insert: Assessment of the CrCl before initiating EVG/c/FTC/TDF • No PRN cases	• ↓number of women • No patients with eGFR< 70 mL/min
Sax et al., 2012[49] *[Study GS-US-236-0102]* **RCT** phase 3, double-blind, parallel assignment, non-inferiority trial (**week 48** results)	700 treatment naïve, ≥18 years, HIV RNA ≥ 5000 c/mL, any CD4 cell count, eGFR> 70 mL/min 348 with EVG/c/FTC/TDF	EVG/c/FTC/TDF vs EFV/FTC/TDF with matching placebos	Primary endpoint at week 48: (EVG/c/FTC/TDF vs EFV/FTC/TDF) **% HIV RNA <50 c/mL** (by ITT, snapshot analysis, NI margin= 12%, 95% power): 87.6% vs 84.1% (difference 3.6%, 95%CI –1.6% to 8.8%) (EVG/c/FTC/TDF QD is virologically non inferior to EFV/FTC/TDF. Similar results in different subgroups) Other endpoints:	• AEs most frequents (≥10%): diarrhea, nausea, fatigue, upper respiratory infection, neuropsychiatric AEs, rash • Discontinuation due to AEs: 4% vs 5% (EVG/c/FTC/TDF vs EFV/FTC/TDF) • Incidence of AEs similar except for neuropsychiatric and rash AEs (more frequent with EFV/FTC/TDF), and nausea (more frequent with EVG/c/FTC/TDF)	• ↓number of women • No patients with eGFR< 70 mL/min

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
	352 with EFV/FTC/TDF		• Mean CD4 cells/mm3 increase at week 48: + 239 (EVG/c/FTC/TDF) vs + 206 (EFV/FTC/TDF), p= 0.009 (Statistically significant CD4 cell count increase in EVG/c/FTC/TDF at week 48) • Virologic suppression more rapid with EVG/c/FTC/TDF • Virologic resistance infrequent	• Median increase in serum Cr (13 vs 1 µmol/l; p<0.001) and decreased eGFR (-14.3 vs -3.0 mL/min) more prominent with EVG/c/FTC/TDF vs. EFV/FTC/TDF • 5 patients on EVG/c/FTC/TDF discontinued for renal AEs (1 increase in Cr and 4 PRN) • HDL cholesterol and total and LDL cholesterol increase in EFV/FTC/TDF arm	
RPV/FTC/TDF (Complera) vs **EFV**/FTC/TDF (Atripla)					
Van Lunzen et al., 2016[53] [STaR study] **RCT**: Non-inferiority, multicenter, international, open-label trial (superiority was tested when non-inferiority was demonstrated) (**Week 96** results)	786 ART treatment naïve HIV-1-infected adults with HIV RNA> 2500 copies/ml at screening; with sensitivity to EFV, FTC, and TDF, and absence of the RPV resistance at entry (i.e. K101E/P, E138A/G/K/Q/R, Y181C/I/V, and H221Y mutations); eGFR > 50 ml/min	**RPV**/FTC/TDF vs. **EFV**/FTC/TDF Each arm consisted of single tablet regimens with administration instructions to take with a 500kcal meal for the RPV group and to take on an empty stomach for EFV group	**Primary Endpoint** • Successful virological suppression (HIV-1 RNA < 50 copies/mL) at week 96 (using Snapshot algorithm, NI margin=12%) RPV vs. EFV (77.9% vs. 72.4%, difference 5.5%, 95% CI:-0.6 to 11.5%; superiority test P-value: 0.076) (Non-inferiority was demonstrated. Superiority was tested, however, was not statistically significant) **Stratified Groups:** 1. By baseline HIV RNA • Baseline HIV RNA ≤100,000 copies/mL RPV 78.8% vs. EFV 71.2% at week 96; difference 7.2%, 95% CI -1.1–13.4% (Statistically significant difference in virological suppression favoring RPV group. Superiority demonstrated: p=0.046) • Baseline HIV RNA >100,000 copies/mL RPV non-inferior to EFV group, however, not superior. • Baseline HIV RNA 100,000 to 500,000 copies/mL: RPV non-inferior to EFV • Baseline HIV RNA >500,000/mL: The non-inferiority margin was not met 2. By baseline CD4 Count • CD4 baseline >200 cells/µl;	**Treatment-emergent Adverse Events (TEAEs)** • Grade 3-4 TEAEs: RPV 10.2% vs EFV 16.6% • Pooled nervous system events (dizziness, somnolence, headache) favored RPV (RPV 27.2% vs. EFV 47.4%, p<0.001) • Pooled psychiatric events (abnormal dreams, depression, anxiety, insomnia) favored RPV (RPV 28.2% vs. EFV 49%, p< 0.001) • Rash events: favored RPV (RPV 15.7% vs. EFV 24.2%, p= 0.003) • Study drug discontinuation due to AEs favored RPV (RPV 3.0% vs. EFV 11.0%, p<0.001) • Mean changes in fasting lipids from BL: statistically significant differences in most lipid measures (TC, LDL, HDL) with the exception of TGs favored RPV • Mean changes in CrCl from BL: favored EFV (RPV -5.4ml/min vs. EFV +4.6ml/min, p<0.0001)	• Open-label design • Most of patients were male (93%) and white (67%)

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
			RPV 80.6% vs EFV 73%; superiority test p-value=0.018 (Non-inferiority demonstrated; statistically significant difference favoring RPV, superiority demonstrated: p=0.018) • CD4 baseline ≤200 cells/µl: The non-inferiority margin was not met	(Better safety profile in RPV groups with the exception of CrCl that was better in EFV group)	
DTG + ABC/3TC (future Triumeq)* vs **EFV/FTC/TDF** (Atripla)					
Rutherford et al., 2016[54] **Systematic Review** of 2 RCTs (SINGLE and SPRING-1). Data extracted from SINGLE study at week 96 and 144 ONLY	833 HIV-1 infection treatment naïve, ≥18 years, HIV RNA ≥ 1000 c/mL, no genotypic resistance, HLA-B*5701 negative 414 to DTG + AB/3TC 419 to EFV/FTC/TDF	**DTG + ABC/3TC** vs **EFV/FTC/TDF** (standard of care)	Primary endpoint at W144: • **Viral suppression to non-detectable (<50 c/mL) at W144** RR = 1.13, 95%CI **1.02** to **1.24** (Virologic superiority of DTG + ABC/3TC at W144) Secondary endpoints at W144: • **CD4⁺ cell count recovery at W144**: > in DTG arm that EFV arm (mean difference: **+46.9** cells/mm³, 95% CI= +15.56 to +78.24) (Better immunologic recovery for DTG + ABC/3TC at W144) • **Resistance**: No antiviral resistance in DTG arm vs 10 in EFV arm	Primary endpoints: (DTG + AB/3TC vs EFV/FTC/TDF): • **Discontinuations due to AEs or death**: • W96: 13 vs 48 events (RR= 0.27; 95%CI **0.15** to **0.50**) • W144: 16 vs 58 events (RR= 0.28; 95%CI **0.16** to **0.48**) (Superiority was shown for DTG + ABC/3TC) • SAEs: 60 vs 65 events (RR= 0.93; **0.68** to **1.29**) (Similar SAEs between groups)	• Includes 1 phase 2 study (SPRING-1) • Only patients from developed countries
Walmsley et al., 2015[56] *[SINGLE study], week 96 and 144 results* **RCT** double-blind, non-inferiority trial with a pre-specified superiority analysis[a] (**week 96** and **144** results)	833 HIV-1 infection treatment naïve, ≥18 years, HIV RNA ≥ 1000 c/mL, no genotypic resistance, HLA-B*5701 negative 414 to DTG + AB/3TC	**DTG + ABC/3TC** vs **EFV/FTC/TDF** (standard of care)	Primary endpoint: • **% HIV RNA <50 c/mL** (ITT, snapshot analysis, NI margin= 10%, 90% power): • *Week 96*: 80% vs 72% (adjusted difference 8.0%, 95%CI 2.3%; 13.8; test for superiority: p=0.006) • *Week 144*: 71% vs 63% (adjusted difference 8.3%; 95%CI 2.0%; 14.6; test for superiority: p=0.01) (Virologic superiority of DTG + ABC/3TC confirmed at W96 and W144) • **Resistance**: No antiviral resistance in DTG arm vs 7 in EFV arm (2 additional cases after W48)	Secondary endpoint: W96 and 144 **Safety outcomes** (DTG + AB/3TC vs EFV/FTC/TDF): • Discontinuations due to AEs (DTG vs. EFV): 3% vs 11% (W96), 4% vs 14% (W144) • Similar safety profile to W48, although more favorable for DTG arm • AEs (EFV vs. DTG): Dizziness (33% vs 7%), abnormal dreams (16% vs 7%), rash (8% vs <1%). Insomnia (10% vs 7%) • SAEs: Low and comparable between groups. 2 new drug-related SAEs: 1	• ↓number of women • ↓number of patients with CD4 cell count <200/mm³ • Non-inferiority study (Not designed to evaluate superiority)

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
	419 to EFV/FTC/TDF			renal failure in EFV arm and 1 osteonecrosis in DTG arm • No new clinically significant changes in clinical chemistry, hematology, or lipid safety parameters • Cr: The nonprogressive, nonclinically meaningful initial increases in serum creatinine levels remain stable for up to 3 years (Safety profile at week 96 and 144 consistent with week 48)	
Walmsley et al., 2013[55] *[SINGLE study]* **RCT** phase 3, double-blind, non-inferiority trial with a pre-specified superiority analysis[a] (**week 48** results)	833 HIV-1 infected treatment naïve, ≥18 years, HIV RNA ≥ 1000 c/mL, no genotypic resistance, HLA-B*5701 negative 414 to DTG + AB/3TC 419 to EFV/FTC/TDF	**DTG + ABC/3TC** vs **EFV/FTC/TDF** (standard of care)	Primary endpoint: • **% HIV RNA <50 c/mL** (ITT, snapshot analysis, NI margin= 10%, 90% power): 88% vs. 81% (adjusted difference +7.4%, 95%CI 2.5%; 12.3, test for superiority: p= 0.003) (Superiority was demonstrated for DTG + ABC/3TC. Also seen in key demographic subgroups and in patients with low or high baseline viral load) Secondary endpoints: • **Time to viral suppression**: shorter median time in DTG arm that EFV arm (28 vs. 84 days, P<0.001) • **CD4⁺ cell count**: > in DTG arm that EFV arm (267 vs. 208 cells/mm^3, p<0.001) (Statistical superiority was demonstrated for DTG + ABC/3TC) • **Resistance**: No antiviral resistance in DTG arm vs 5 in EFV arm	Secondary endpoint: **Safety outcomes** (DTG + AB/3TC vs EFV/FTC/TDF): • Discontinuations due to AEs: 2% vs 10% • AEs: Rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence): more common in EFV arm, except insomnia (15% in DTG arm vs 10% in EFV arm). • SAEs: 9 patients had SAEs related to the study drug: 1 (with HSR) in DTG arm vs. 8 in EFV arm (4 with psychiatric event, 2 drug hypersensitivity, 1 cerebrovascular accident and 1 renal failure) • Cr: Mild, nonprogressive increases in the serum Cr level (DTG + ABC/3TC QD had better safety profile vs EFV/FTC/TDF)	• ↓number of women • ↓number of patients with CD4 cell count <200/mm^3 • Non-inferiority study (Not designed to evaluate superiority)
TDF/FTC (Truvada) vs **3TC/ZDV** (Combivir)					
Campbell et al., 2012[58] [PEARLS study]	1042: 517 to 3TC/ZDV+EFV 525 to TDF/FTC+EFV)	**TDF/FTC**+EFV vs **3TC/ZDV**+EFV	Primary efficacy endpoint (median 184 weeks): • **Treatment failures** (composite endpoint: *time to first occurrence of death, disease progression or virologic failure*):	Primary safety endpoint (median 192 weeks): **Safety events** (composite endpoint: *date of onset of grade ≥3, sign/symptom, date of specimen collection of a grade ≥3*	• Relatively health study population (low

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
RCT: Noninferiority, phase 4, parallel assignment and open label trial comparing three-drug combinations (Data extracted from the two-drug combinations of interest ONLY) Setting: ACTG International sites (9 countries in 4 continents: Africa, Asia, South America,US)	HIV infected treatment naïve adult individuals with CD4 lymphocytes <300 cells/ml, and ≤7 d of cumulative ART prior to study entry, recruited from **resource-limited areas**		95 (18.0%) in TDF/FTC vs 98 (18.8%) 3TC/ZDV (HR 0.95, 95% CI 0.72-1.27, p=0.74) (No difference in efficacy between groups) Secondary endpoints: • **Immunologic failure**: No significant differences between groups	*laboratory abnormality, or date of treatment modification*) 243 (46%) in TDF/FTC vs 313 (60%) 3TC/ZDV (HR 0.64, CI **0.54-0.76**; p<0.001) **Grade 3-4 laboratory abnormalities**: HR 0.55, 95% CI **0.43-0.71** , p<0.0001 **Women subgroup**: HR 0.50, CI **0.39–0.64** (TDF/FTC showed superior safety with less laboratory AEs in the overall population and a better safety profile in women than in men in comparison to 3TC/ZDV)	prevalence of comorbidities) • Intense clinical and laboratory monitoring (improved adherence)
Arribas et al., 2008[57] [Study 934] **RCT**: prospective, randomized, multicenter noninferiority study **(Week 144 Results)** Setting: sites in France, Germany, Italy, Spain, the United Kingdom, and the United States	456 HIV infected treatment naïve adult patients with HIV RNA levels >10,000 copies/mL, GFR>50 mL/min	**TDF/FTC**+EFV vs **3TC/ZDV**+EFV	Primary efficacy endpoint: • **% patients with HIV RNA <400 c/mL** (TLOVR; noninferiority if lower bound of the 95% CI for the difference no lower than -13%) 161 (**71**%) of 227 patients in TDF/FTC arm vs 133 (**58**%) of 229 patients in 3TC/ZDV arm; p=0.004 (Noninferiority demonstrated with a statistically significant greater response in TDF/FTC arm) Other endpoints: • **% patients with HIV RNA <50 c/mL:** 146 (**64**%) of227 patients in TDF/FTC arm vs. 130 (**56**%) of 231 patients in 3TC/ZDV arm; p = 0.08). • **CD4 count Increase from BL**: 312 cells/mm^3 in TDF/FTC arm vs. 271 in the ZDV/3TC arm; p=0.09) • **Adherence**: 89% with TDF/FTC arm vs 87% with ZDV/3TC arm; p=0.15 (No significant differences between groups) • **Virologic failure with resistance**: 41% in ZDV/3TC arm vs 29% in TDF/FTC; p=0.004	Safety outcomes • **Discontinuations**: 4 in TDF/FTC vs 10 in ZDV/3TC • **Discontinuations due to AEs**: Only one patients in ZDV/3TC from W96 to W144 • **Discontinuations due to renal AEs**: none • **Serum Cr elevation**: 1 patient in TDF/FTC vs. 2 patients in ZDV/3TC • **> 20% decrease in limb fat**: 15% in ZDV/3TC vs. 5% in TDF/FTC; p=0.01 • **Increase in total cholesterol**: +36 mg/dL in ZDV/3TC vs. +24 mg/dL in TDF/FTC; p=0.005 • **Increase in triglycerides**: +36 mg/dL in ZDV/3TC vs. +4 mg/dL dL in TDF/FTC; p<0.0001	

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
			(statistically significant more failures in ZDV/3TC)	(Renal safety seems to be favorable in both groups. More lipoatrophy and higher increase in total cholesterol and tryglicerides in ZDV groups vs TDF group)	
TDF/FTC (Truvada) vs **ABC/3TC** (Epzicom)					
Hemkens et al., 2015[59] **Systematic Reviews** and **Meta-analysis** of 22 RCTs comparing TDF vs non-TDF regimens (16 RTCs) and TDF/FTC vs ABC/3TC (6 RCTs). Data extracted ONLY from the 6 TDF/FTC vs ABC/3TC RCTs (A5202, A5224s, ASSERT, HEAT, Epzicom-Truvada study, SINGLE)	4165 treatment naïve adult patients	**TDF/FTC** vs **ABC/3TC** plus a third ARV agent	Endpoints: TDF/FTC vs ABC/3TC * **Mortality:** RR 1.25 (95%CI 0.47, 3.31) * **AIDS**: RR 0.77 (95%CI 0.52, 1.14) * **Fractures**: RR 1.09 (95%CI 0.73, 1.63) *** Virological failure** (snapshot analysis or TLOVR). RR for being free of virological failure (HIV-1-RNA levels <50 copies/mL): RR 1.02; 95%CI 0.95–1.10 * **CD4 cell counts:** RR -18.40; 95%CI - 39.77 to 2.97, p<0.01 but high heterogeneity (TDF/FTC vs ABC/3TC) (No significant differences between groups)	Lipid outcomes at week 48: TDF/FTC vs ABC/3TC Mean difference (95%CI): * LDL-cholesterol -11.42 mg/dl (**-15.56, -7.28**) * HDL-cholesterol -3.29 mg/dl (**-5.60, -0.98**) * Total Cholesterol -19.89 mg/dl (**-24.97, -14.80**) * Triglycerides -26.12 mg/dl (**-37.82, -14.43**) Renal outcomes at week 48: TDF/FTC vs ABC/3TC * **eGFR**: mean difference (95%CI): RR-0.77 (-2.92, 1.39) (No significant differences between arms) Bone outcomes at week 48: TDF/FTC vs ABC/3TC BMD mean difference (95%CI): * **BMD hip**: RR -1.62% (**-2.28, -0.96**); * **BMD lumbar spine**: RR -1.35% (**-2.26, -0.45**) (TDF/FTC favored lipid outcomes. Worse safety profile due to more BMD reductions in TDF/FTC vs ABC/3TC)	• Third ART-compound different between groups (EFV or boosted PI) • Heterogeneity in virological failure analysis • Biomarker assessment at week 48 only • No data about discontinuation • High risk of bias of RCTs
Cruciani et al., 2014[80] **Systematic Reviews** and **Meta-analysis** of 30 RCTs conducted from 1996 to 2013. Data extracted from 6 RCTs that compare	Week 48: 4118 HIV-1 infected adult patients (6 trials) Week 96: 2003 HIV-1 infected adult patients (4 trials)	**ABC/3TC** vs **TDF/FTC** plus a third ARV agent	Primary endpoints: ABC/3TC vs TDF/FTC • **% subjects with HIV RNA <50 c/mL at W48:** RR 0.98; 95% CI 0.94–1.03; p=0.5 Low BL viral load strata: RR 1.01; 95% CI 0.99–1.03; p=0.19 High BL viral load strata: RR 0.96; 95% CI 0.90–1.03; p=0.22 (Similar efficacy results at W48 regardless of BL viral load. Similar results at W96)	Safety outcomes: ABC/3TC vs TDF/FTC Discontinuations due to AEs: RR 1.26; 95% CI 0.99–1.61; p=0.06 (Similar results between groups)	Not reported

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
ABC/3TC and TDF/FTC					
Sax et al., 2011[61] [ACTG A5202: Final Results] **RCT**, phase 3, parallel assignment, blinded equivalence study	1864 HIV-infected treatment-**naive** patients. Stratification: 1060 to **low HIV RNA stratum** (HIV screening RNA <10^5 copies/mL) 797 to **high HIV RNA stratum** (HIV screening RNA ≥10^5 copies/mL)	**ABC/3TC** vs **TDF/FTC** plus EFV or ATV/r	Primary endpoints: *Low HIV RNA stratum:* • **Time to virologic failure** (confirmed HIV RNA level >1000 copies/mL at or after 16 weeks and before 24 weeks, or ≥200 copies/mL at or after 24 weeks): 1. ***ATV/r group***: ABC/3TC vs TDF/FTC HR 1.25 (95% CI 0.76, 2.05), 35 vs 29 patients with virologic failures. Post-hoc analysis: 88.3% and 90.3% patients without virologic failure at week 96, difference of -2.0% (95% CI -7.5, 3.4) 2. ***EFV group***: ABC/3TC vs TDF/FTC HR 1.23 (95% CI 0.77, 1.96), 39 vs 33 patients with virologic failures. Post-hoc analysis: 87.4% and 89.2% patients without virologic failure at week 96, difference of -1.8% (95%CI:-7.5, 3.9) (Similar efficacy between groups with ATV/r and EFV) • **Time for first regimen modification**: ATV/r: ABC/3TC vs TDF/FTC, HR 1.43 (95% CI, 1.06, 1.92, P= 0.018) EFV: ABC/3TC vs TDF/FTC, HR 1.48 (95% CI, 1.12, 1.95, P= 0.005) (Shorter time for ABC/3TC with both ATV/r and EFV) Secondary endpoints: • **% patients with HIV RNA <50 copies/mL at week 96**: 1. ABC/3TC+ATV/r vs TDF/FTC+ATV/r: 89% vs 93%, difference of -4.6% (95%CI -9.9, 0.8) 2. ABC/3TC+EFV vs TDF/FTC+EFV: 91% vs 92%, difference of -0.6% (95%CI -6.0, 4.8) • **Time to regimen failure**: (HR 1.40; 95% CI, 1.05, 1.87, P 5 .02) or EFV (HR 1.44; 95%CI, 1.09, 1.89; P= 0.01	Primary endpoints: *** Time to first safety event**: **ATV/r**: time not significantly different for ABC/3TC or TDF/FTC (HR 1.13; 95% CI, 0.83 to 1.54, P=0.44) **EFV**: shorter time for ABC/3TC than TDF/FTC (HR 1.38; 95% CI, 1.03, 1.85, P=0.03) (shorter time for ABC/3TC with EFV) Other endpoints: **Deaths**: 10 (4 ATV/r+ABC/3TC), 3 (EFV+ABC/3TC), 3 (EFV+TDF/FTC) **CV AEs**: infrequent in all arms **Bone fractures**: 3% in ATV/r+ABC/3TC, 4% ATV/r+TDF/FTC, 6% EFV+ABC/3TC, 5% EFV+TDF/FTC **Lipid levels**: Median changes of lipid levels for ABC/3TC vs TDF/FTC at week 48: 1. With ATV/r * total cholesterol: 30 vs 8 mg/dL (P<0.001) * LDL cholesterol, 14 vs 0 mg/dL (P<0.001) * HDL cholesterol, 7 vs 4 mg/dL (P<0.001) * triglycerides, 27 vs 14 mg/dL (P=0.004) 2. With EFV: * total cholesterol: 34 vs 19 mg/dL (P<0.001) * LDL cholesterol, 17 vs 6 mg/dL (P<0.001) * HDL cholesterol, 12 vs 9 mg/dL (P=0.006) * triglycerides, 12 vs 13 mg/dl (p=049) (More favorable lipid profile in TDF/FTC compared to ABC/3TC. Similar results at week 96) **Renal AEs**:	

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
			(Shorter time to regimen failure for ABC/3TC than TDF/FTC with ATV/r) • **CD4 Cell Count Changes**: ATV/r: week 48 (median 170 ABC/3TC and 157 TDF/FTC); week 96 (240 and 241), p>0.6 EFV: week 48 (median 175 ABC/3TC vs 147 TDF/FTC); week 96 (227 vs 200), p=0.035 *High HIV RNA stratum:* **Times to virologic failure:** faster with ABC/3TC with both ATV/r and EFV (higher rate mutations in ABC/3TC group)	Mean change from BL in CrCl: ABC/3TC vs TDF/FTC with ATV/r: W48: +3.3 mL/min vs -3.1 mL/min (p<0.001) W96: +5.2 mL/min vs -3.1 mL/min (p<0.001) (Greater CrCl decreased in TDF/FTC vs ABC/3TC with ATV/r. No differences with EFV) **Adherence**: High (no significant difference between ABC/3TC and TDF/FTC with EFV or ATV/r, p≥0.14) High RNA stratum: **Safety, tolerability and adherence**: (safety favored TDF/FTC over ABC/3TC)	
Smith et al., 2009[62] [HEAT study] **RCT** double-blind, placebo-matched, multicenter, noninferiority trial	688 HIV-1 infected antiretroviral-**naive** patients	**ABC/3TC** vs **TDF/FTC** plus LPV/r	Primary endpoint: **% patients with HIV-1 RNA <50 copies/ml at week 48** (NI margin= -12%): • ITT-E analysis: 68% patients in ABC/3TC vs. 67% in TDF/FTC (95%CI on the difference -6.63 to 7.40, P=0.913) • TLOVR analysis: 63% in ABC/3TC vs. 61% in TDF/FTC (Non-inferiority was demonstrated) At week 96, non-inferiority was maintained: 60% ABC/3TC vs 58% TDF/FTC Secondary endpoints: • Similar efficacy by BL viral load strata (< or ≥100000 c/ml) and by CD4 cell count at week 48 and 96 • CD4 increased (ABC/3TC vs. TDF/FTC, cells/µl): +250 vs. +247 by week 96	Primary endpoint: • **% patients with AEs over 96 weeks** (ABC/3TC vs TDF/FTC): - % of grade 2-4 AEs: 80% vs 80% - % of grade 2-4 drug-related AEs: 50% vs 46%. Most common= diarrhea (19% both groups). - % drug-related SAEs: 18 (5%) vs 10 (3%) - Suspected ABC HSR: 14 patients (4%) in ABC arm and 3 (<1%) in TDF arm - Withdrawal due to AE: 6%, both groups. Most common AEs leading to discontinuation: GI AEs in TDF/FTC and lipid abnormalities in ABC/3TC Other safety endpoints **Renal outcome**: • Discontinuations: 2 patients with acute renal failure discontinued from TDF/FTC arm • Progression to more advanced CKD: 11 in TDF arm vs 4 patients in ABC arm **Lipid outcomes**:	

Study Reference and Design	Number and type of Patients selected	Treatment Interventions	Clinical Efficacy	Clinical Safety	Limitations
				• ↑ in total cholesterol, triglycerides, and LDL observed among patients receiving ABC/3TC. • HDL ratio unchanged in both groups • Need of lipid lowering medication: 20% in ABC arm vs 15% in TDF arm **CV AEs**: Few AEs and none related to study drug (Both backbones are well tolerated with similar treatment rates of discontinuations. Lipid profile favored TDF arm and renal profile favored ABC arm)	

* All the SR, MA and RCTs included in Appendix B assess the efficacy and safety of one fixed-dose combination versus another fixed-dose combination as part of a combination regimen or as a complete regimen for initial treatment of HIV in treatment naïve patients.

Key to Abbreviations: 3TC = lamivudine; β2M/Cr= β2-microglobulin/Cr; ABC = abacavir; AE= Adverse Event; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BL= baseline; BMD= Bone mineral density; COBI or c = cobicistat; cART= combination antiretroviral therapy; CKD= chronic kidney disease; Cr= creatinine; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR-CG= estimated glomerular filtration rate which was calculated by Cockcroft–Gault equation; EVG = elvitegravir; FTC = emtricitabine; FDA= Food and Drug Administration; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR= Hypersensitivity reaction; LDL= low-density lipoprotein; NI=non-inferiority; PI= protease inhibitor; PRN= proximal renal tubulopathy; RAL = raltegravir; RBP/Cr=retinol binding protein/Cr; RCT: randomized controlled trial; RPV = rilpivirine; RR_{MHRE}=Mantel-Haenzel random effects relative risk; RTV = ritonavir; TAF= tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TLOVR= time-to loss-of-virological-response analyses; UPCR= urinary protein/Cr, UACR= urinary albumin/Cr; WMD_{RE}= random effects weighted mean difference, W= Week; ZDV = zidovudine

Appendix D. List of excluded references

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